DISTILLATION

# Manufacturing Chemist

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A PUBLICATION OF THE LEONARD HILL TECHNICAL GROUP

Vol. XXXII No. 8

AUGUST 1961

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The mastery of Rubens lay in the great vitality he gave to his subjects; beauty for him was a living thing. For the cosmetic technologist today, it is an exacting modern science. Helping him in the development of new and improved beauty preparations is the Bisomel range of high-grade chemicals.

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This is widely used as a non-greasy alternative to vegetable or mineral oils in many water-in-oil emulsions. In oil-in-water emulsions, it imparts a soft, velvety feel to the skin. In conjunction with a microcrystalline wax in heavily-pigmented and water-free preparations, isopropyl myristate has a thixotropic effect which improves adhesion to the skin. *Full technical and commercial information on request.*

*Rubens' portrait of Helene Fourment (detail) by permission of the Trustees of the National Gallery*

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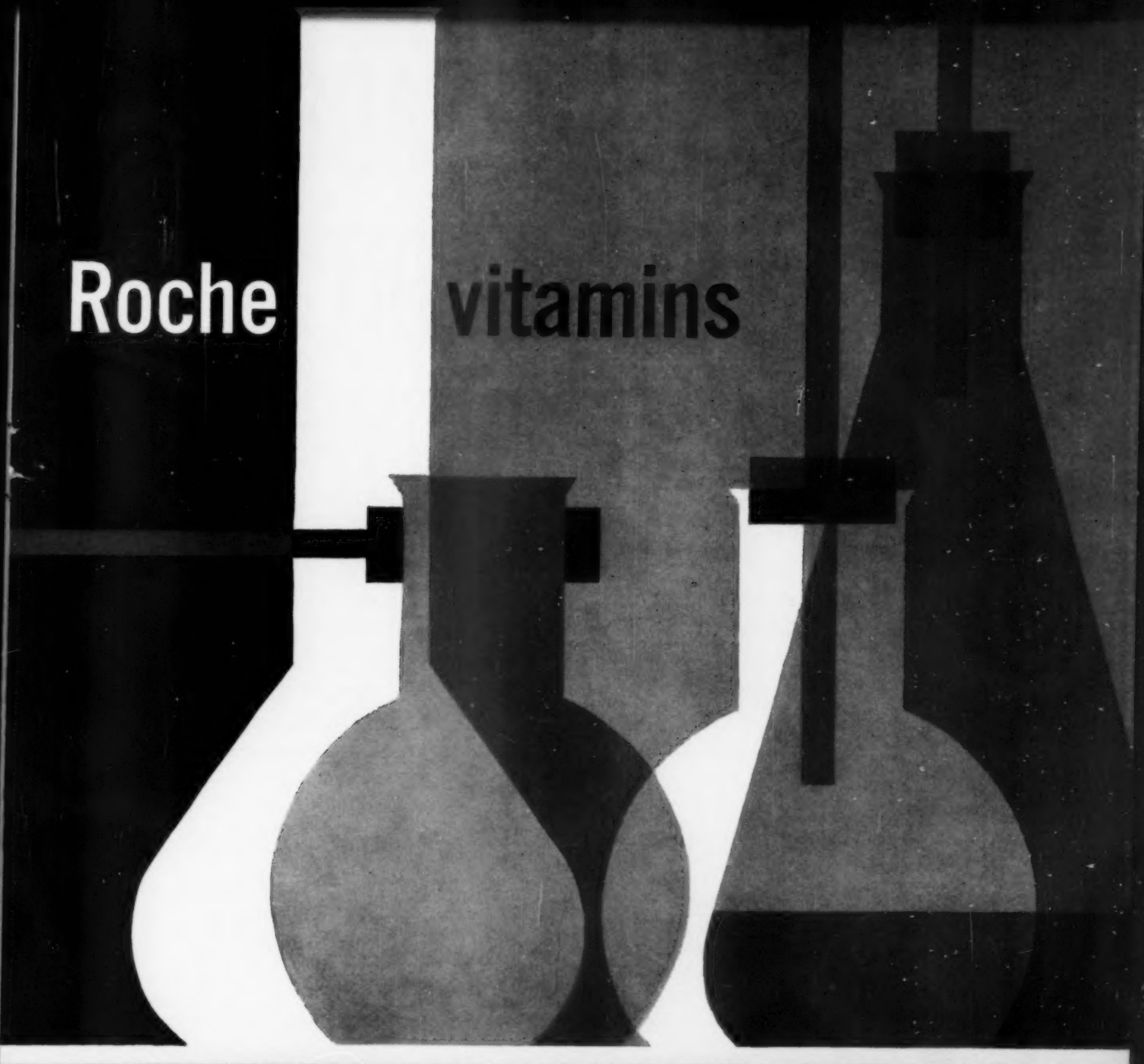

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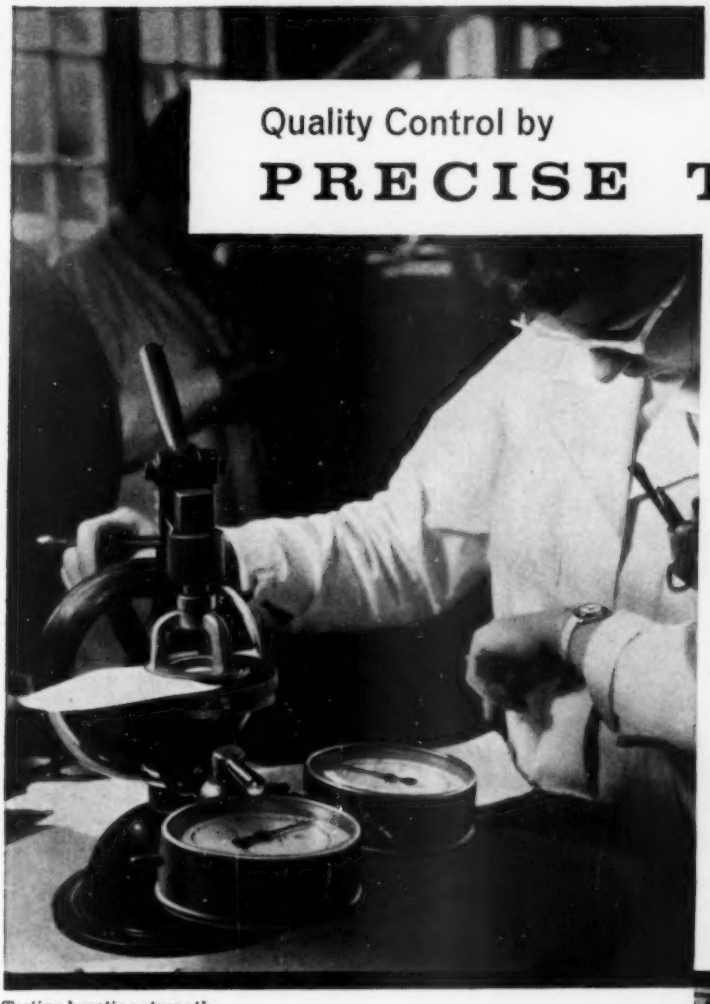

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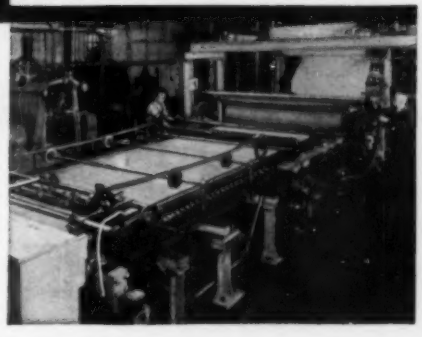

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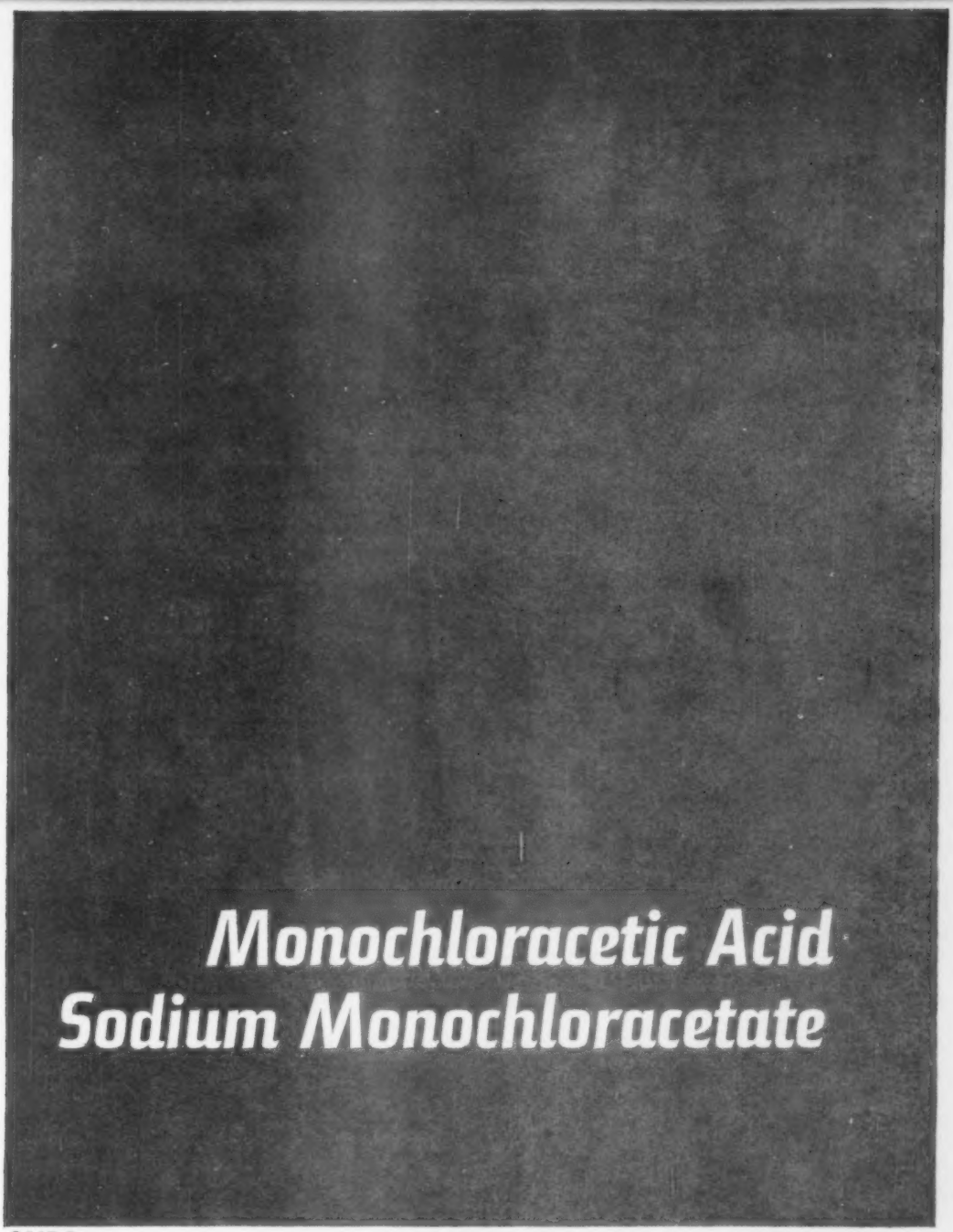


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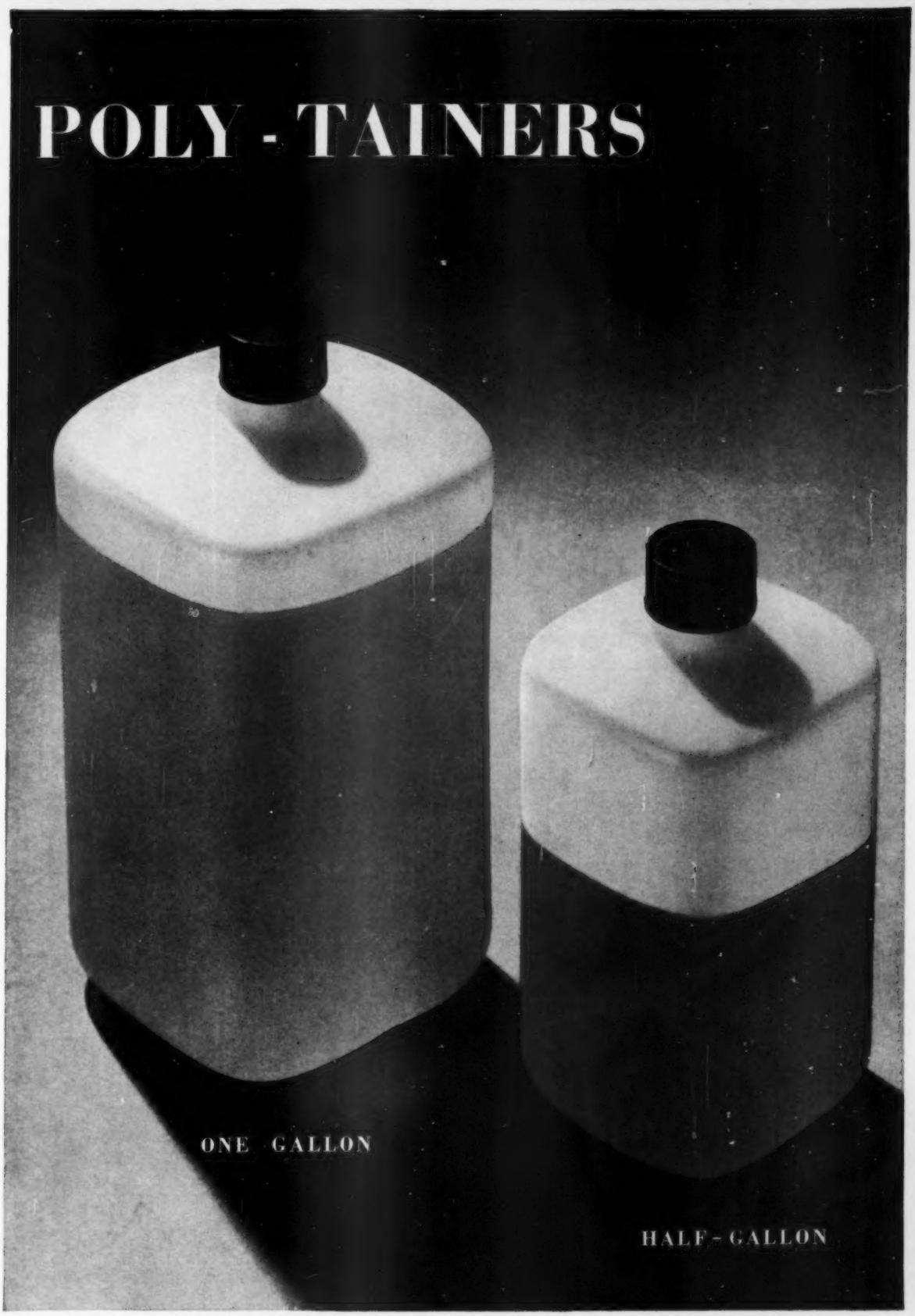


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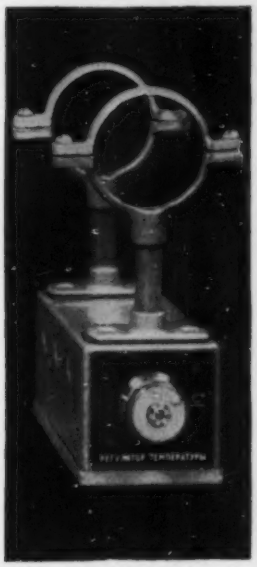

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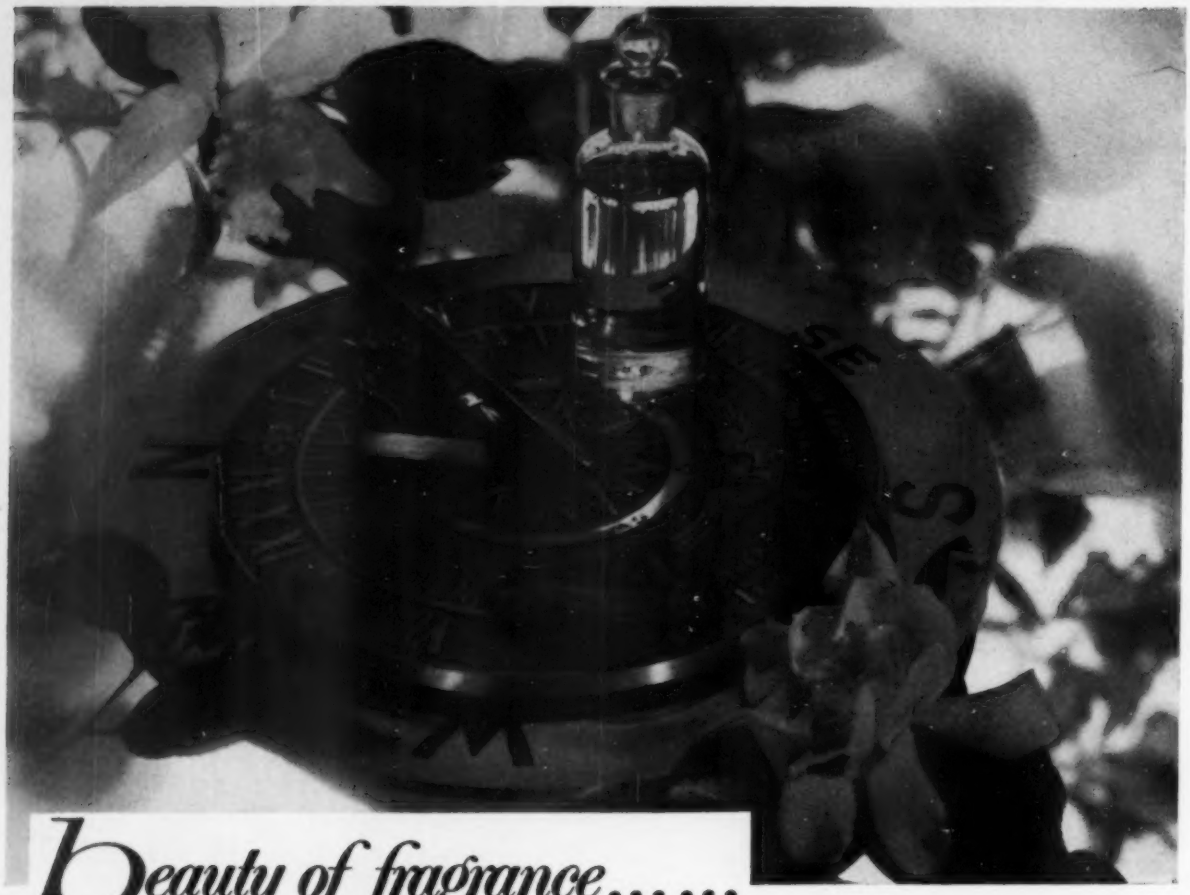

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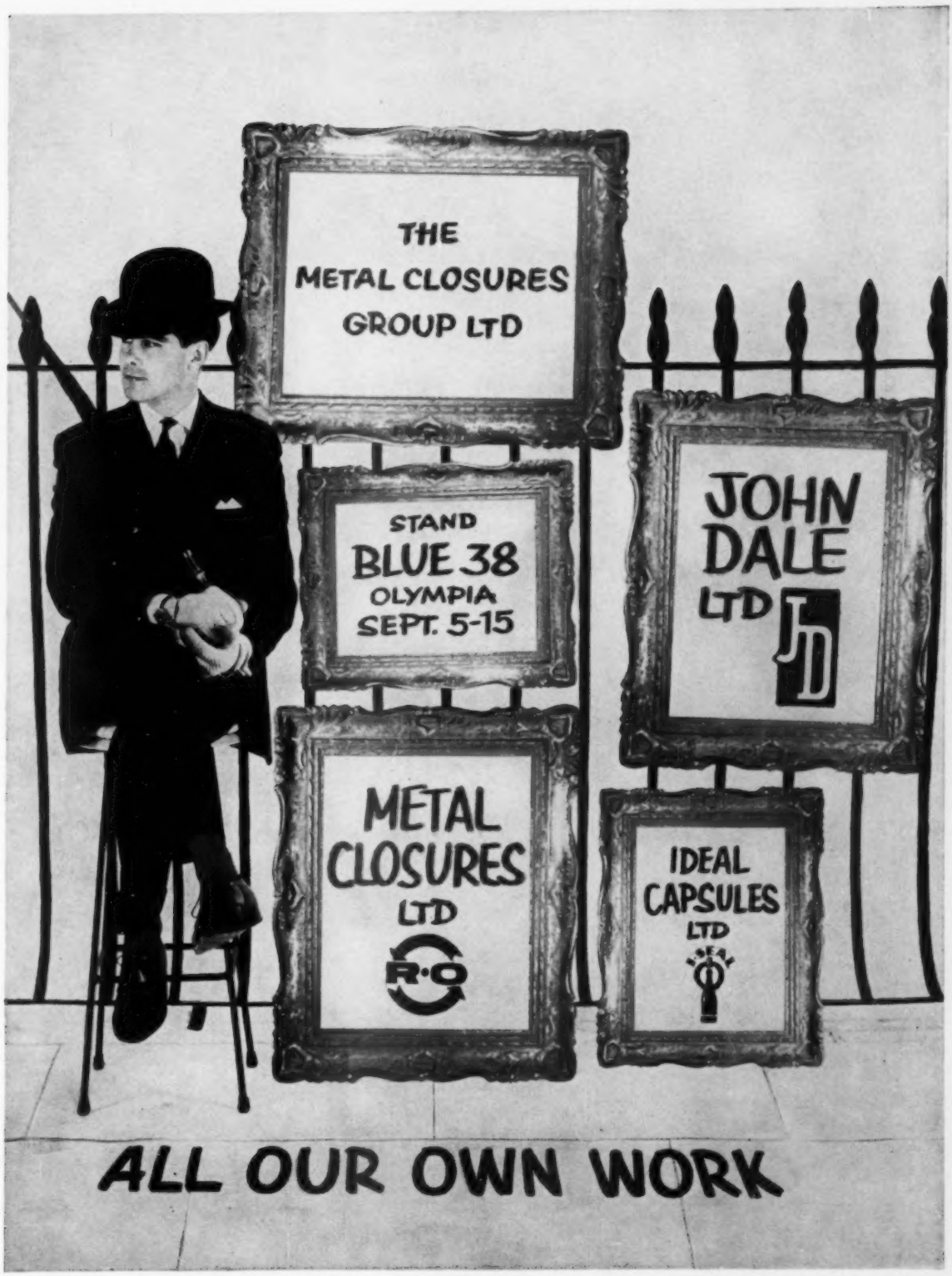
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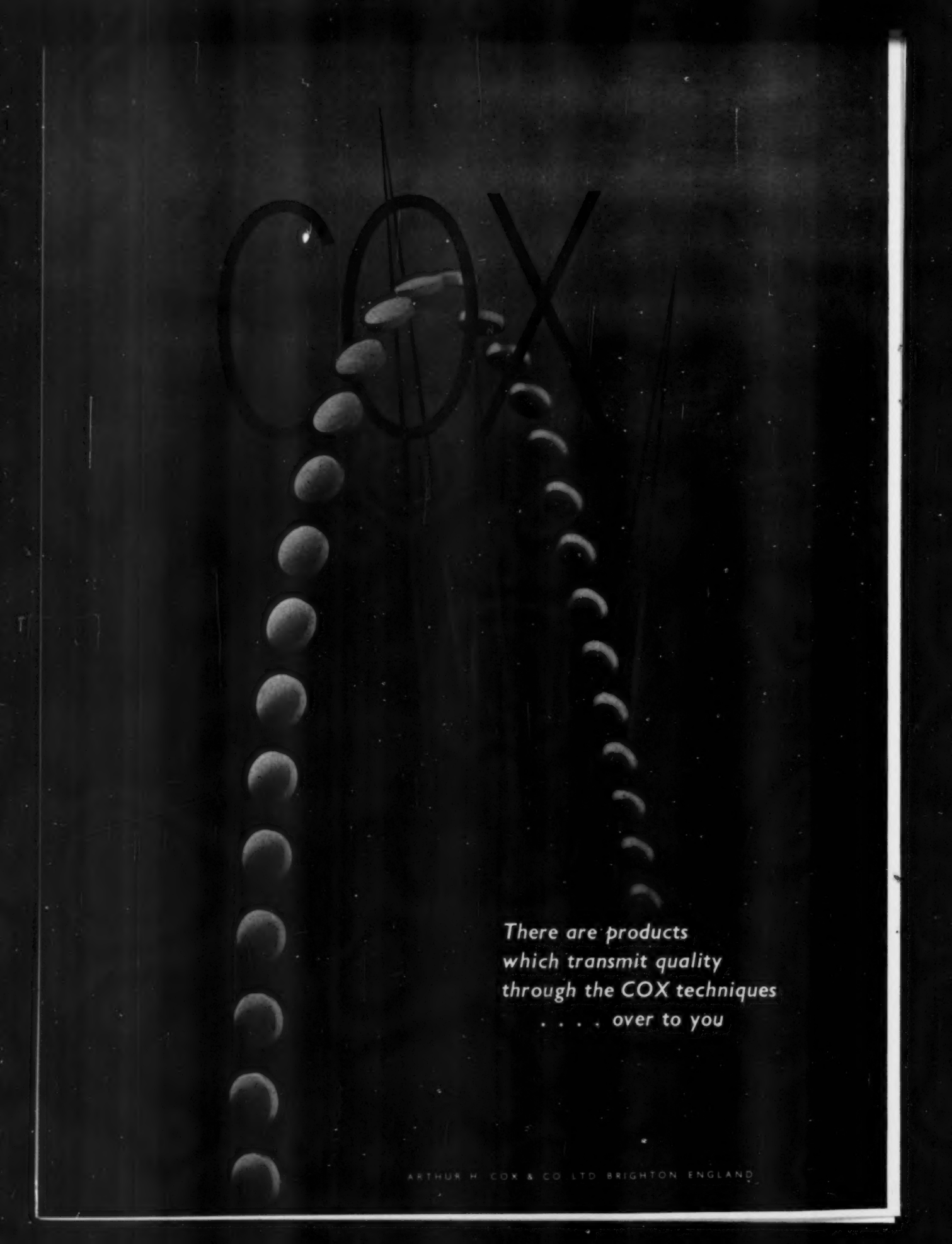
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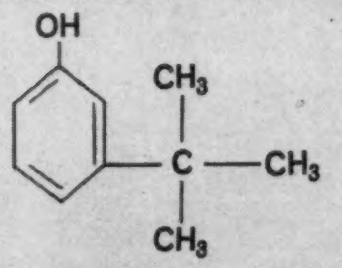


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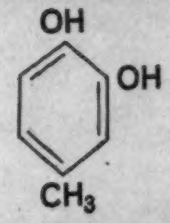


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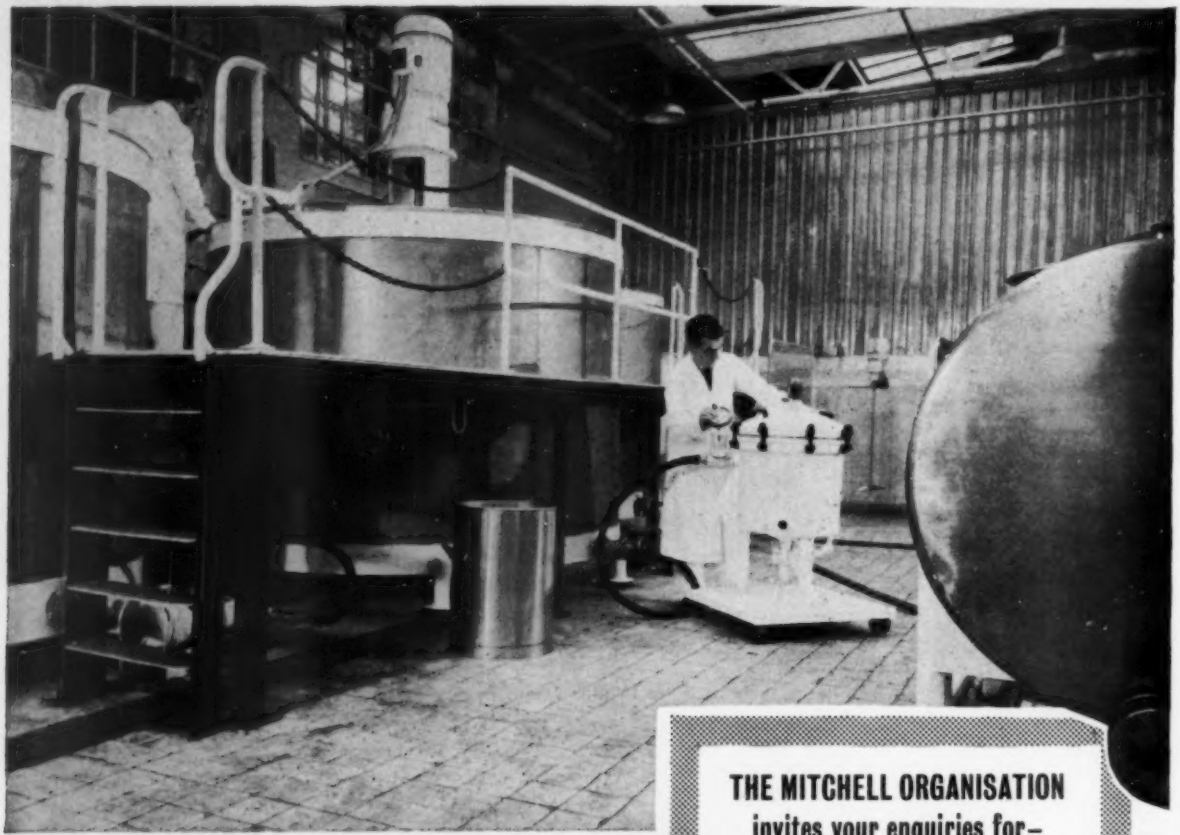
*(Photograph by courtesy of Evans Medical Ltd., Speke, Liverpool)*



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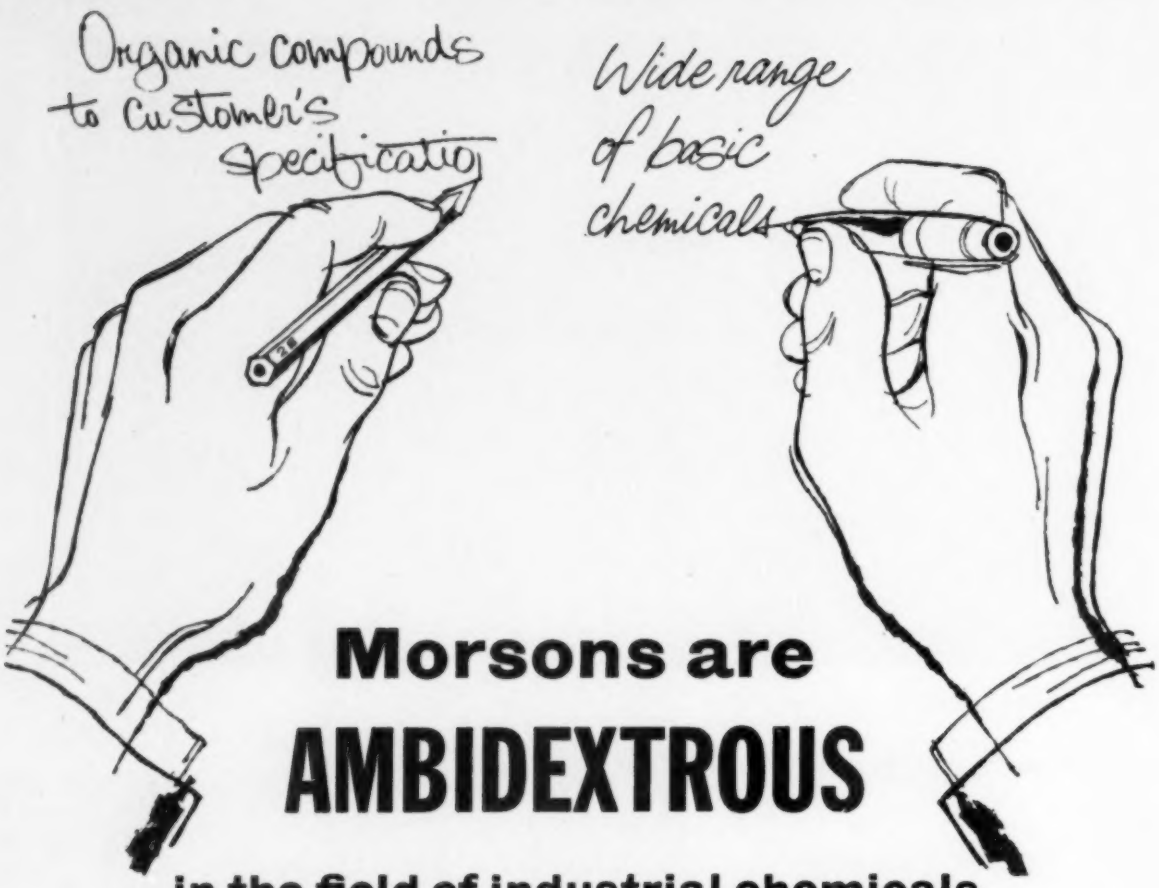


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## in the field of industrial chemicals

On the one hand, Morsons are well-equipped with the right plant and technical "know-how" to manufacture organic compounds to customers' own specifications (after all, they have been doing just this for over one hundred years).

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IODINE B.P.
IODOFORM B.P.C. 1954
POTASSIUM IODATE
POTASSIUM IODIDE B.P.
POTASSIUM IODIDE/CALCIUM STEARATE
SODIUM IODIDE B.P.

OXALIC ACID RECRYST
AMMONIUM OXALATE
FERRIC AMMONIUM OXALATE
POTASSIUM OXALATE

PHENOLPHTHALEIN, AMORPHOUS

SODIUM PHENOLSULPHONATE B.P.C. 1949
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POTASSIUM PHOSPHATE B.P.C. 1949
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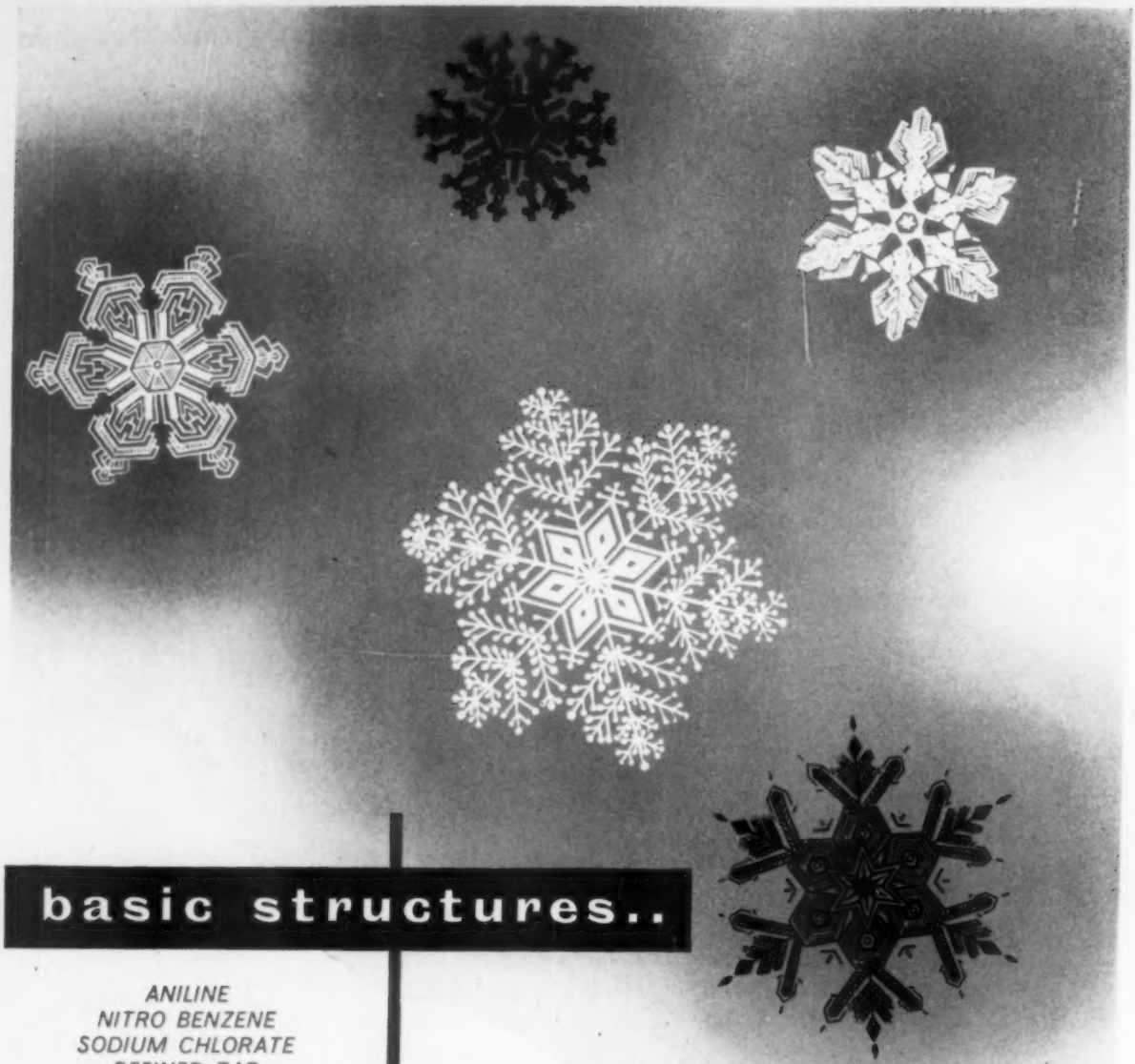

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**SHEFFIELD** Richmond Park Road, Handsworth, Sheffield 13. (Sheffield 49365)

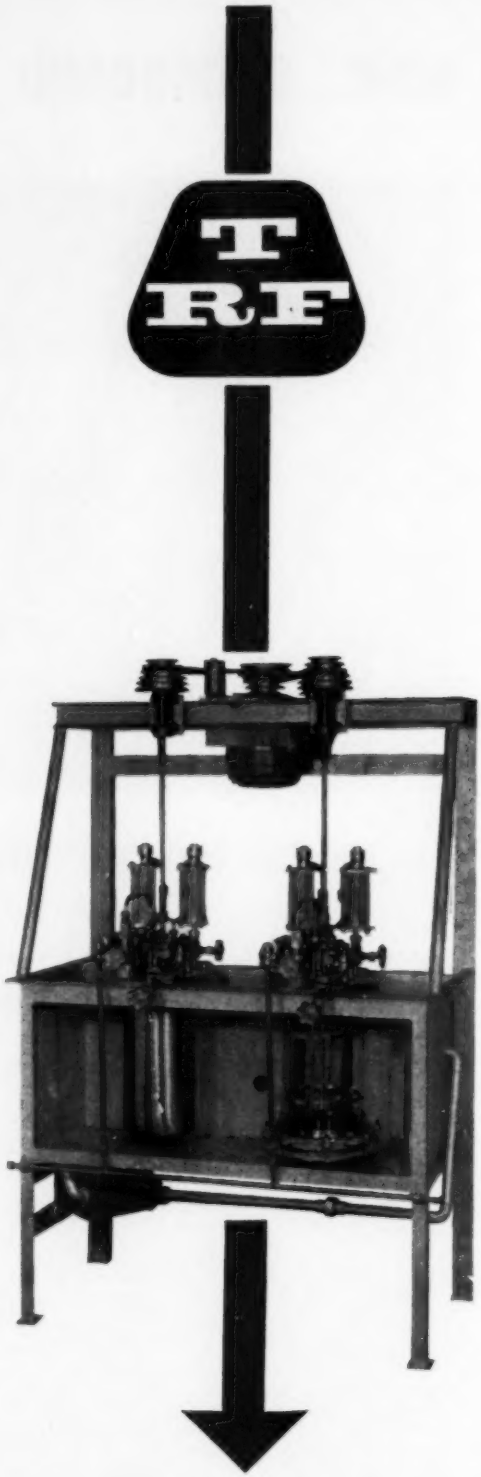
**LONGTON** 482 Uttoxeter Road, Longton, Staffs. (Stoke-on-Trent 33328)

**PORTSMOUTH** Rodney Road, Fratton Industrial Estate, Fratton, Portsmouth Hants. (Portsmouth 32373)

**SUNDERLAND** Pallion Trading Estate, Sunderland, Co. Durham. (Sunderland 57760)

**MANCHESTER** Leestone Rd., Wythenshawe, Manchester 22. (Wythenshawe 3441)

# ONE STEP AHEAD

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welcome enquiries for new products, particularly in the petrochemical and cellulose derivative fields.

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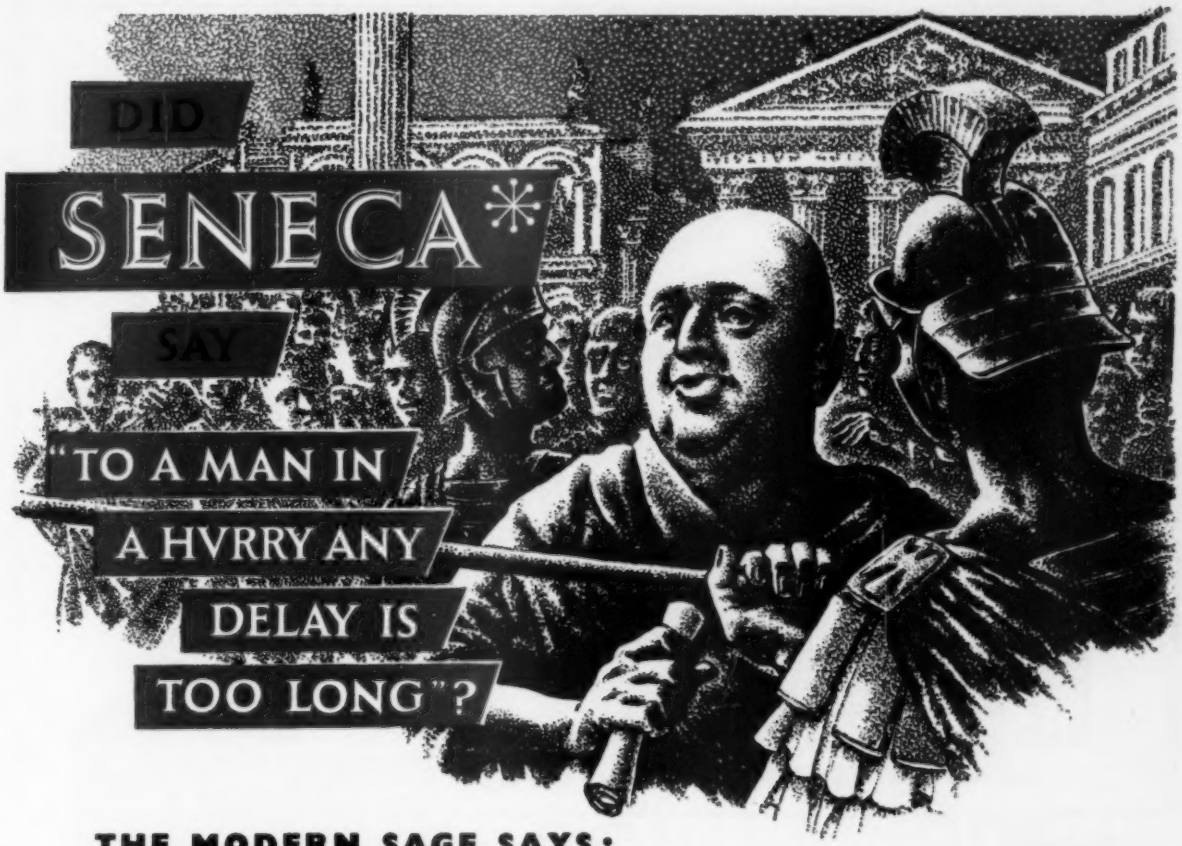


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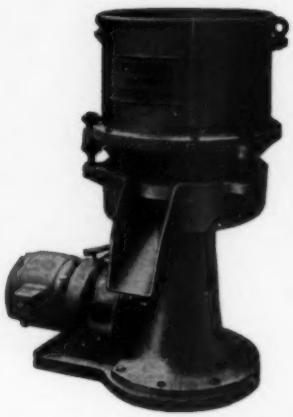

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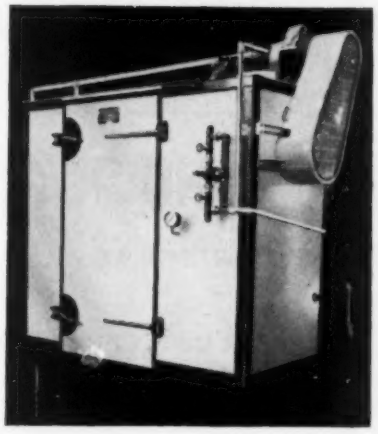
"PRODUCTS OF SCIENTIFIC MERIT"

# too wet or too dry..

## or just right



A Briggs single truck oven—one of the many steam, electrically and gas heated drying ovens in the Briggs standard range.

The weather in these islands is, of course, quite an unknown quantity—and certainly one which is utterly beyond the influence of ordinary mortals.

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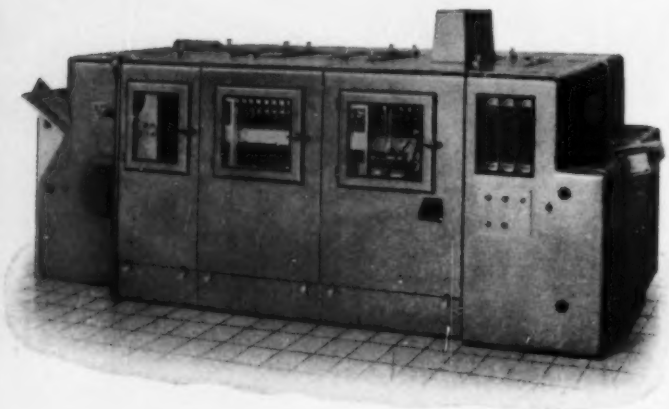
AUTOMATIC AMPOULE HANDLING PLANT Type **HAPE**

*A new way of fully-automatic ampoule handling*

Cleaning, Drying, Sterilizing, Protective Gassing, Filling and Sealing



Depending on number of working stations and on ampoule sizes and liquid used, the plant can be built for outputs ranging between 3,000 and 20,000 units/h.

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THE ROBERTS "STRAITLINE"

MULTIPLE HEAD VACUUM FILLING MACHINE

Nº 714

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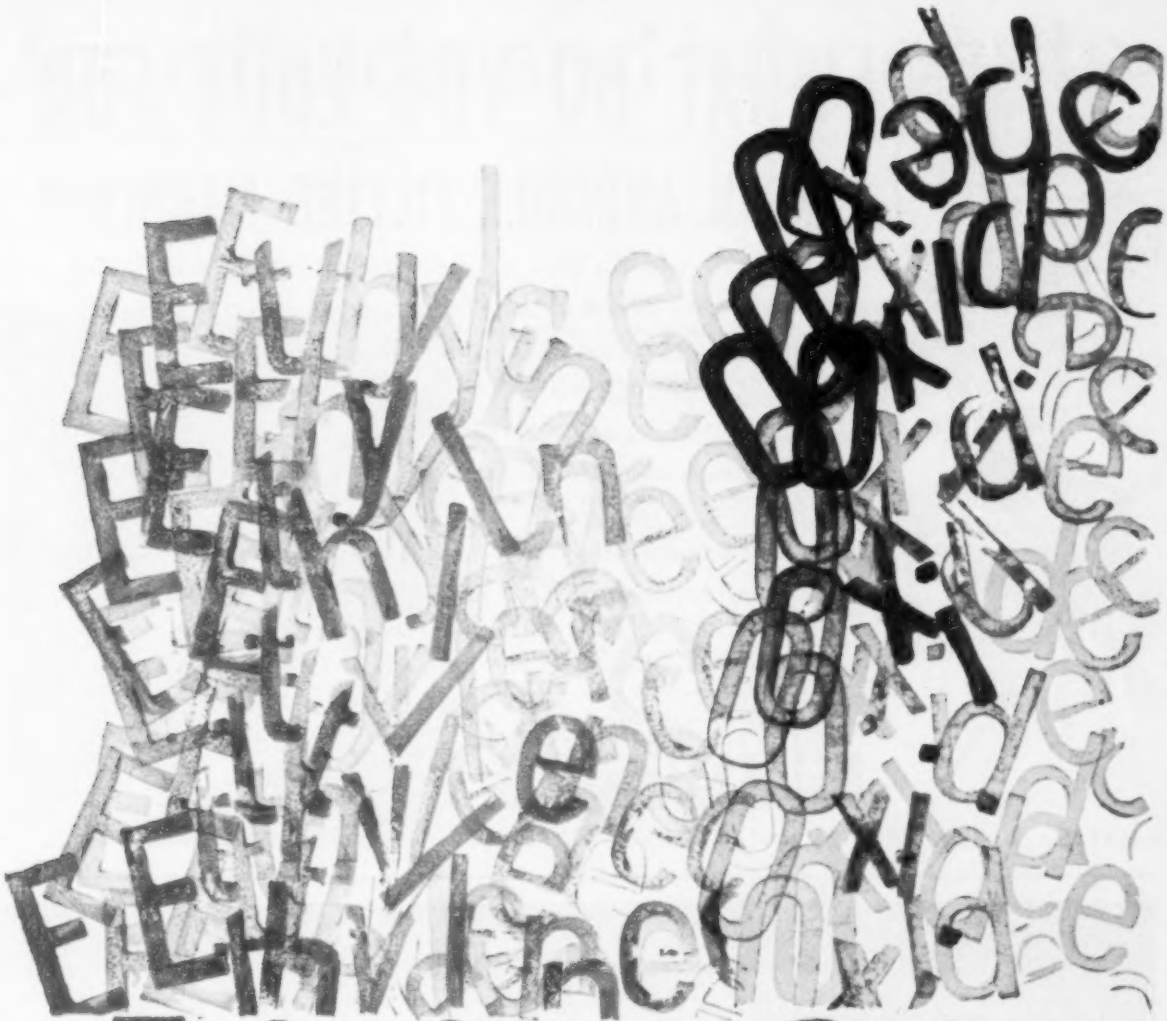
**Phone: Bolton 4925 (2 lines).** **Grams: 'Filling' Bolton.**

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## from SHELL

From Ethylene Oxide, Shell Chemicals make a number of important derivatives including Ethylene Glycols, Ethanolamines and Polyethylene Glycols.

If you are interested in Ethylene Oxide as a basic raw material for your process, it is freely available from Shell Chemicals, in cylinders or bulk, to a high degree of purity and consistent quality.

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GC/18

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- *Filling adjustable while machine is running*
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- *Compact overall dimensions*

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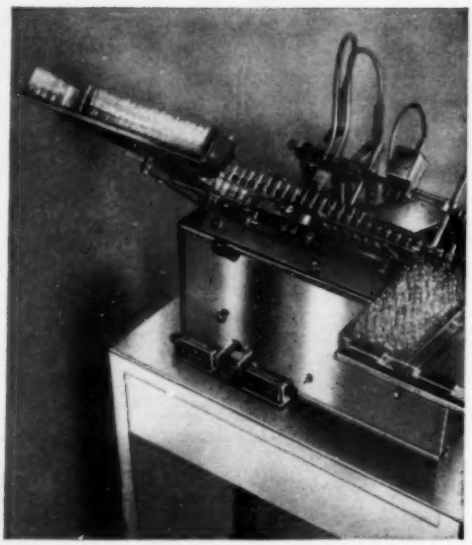

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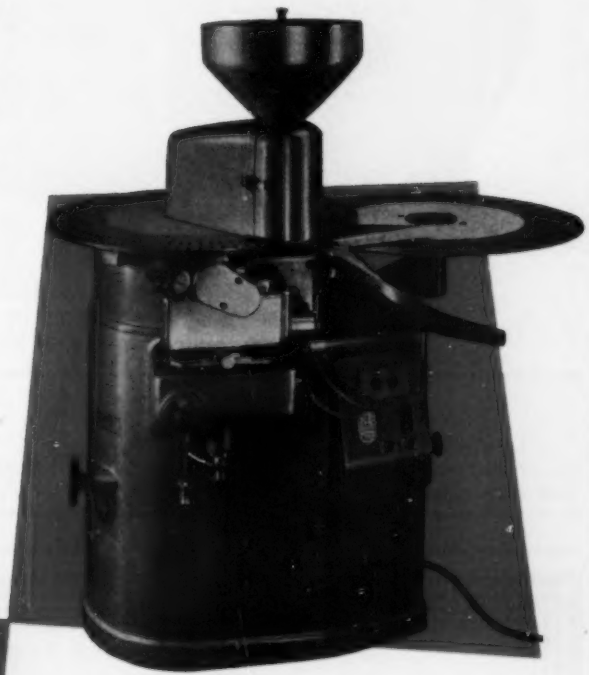

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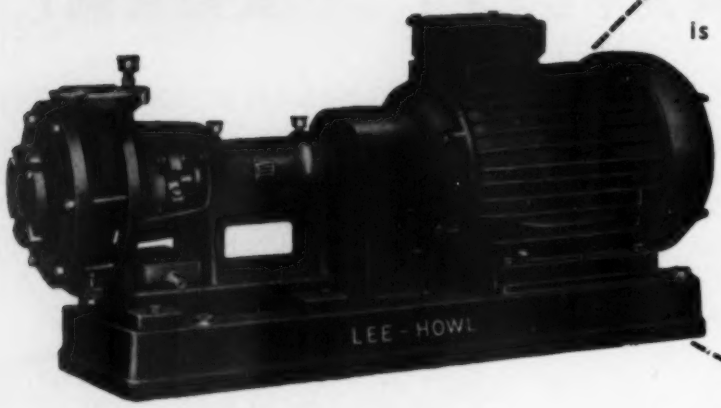


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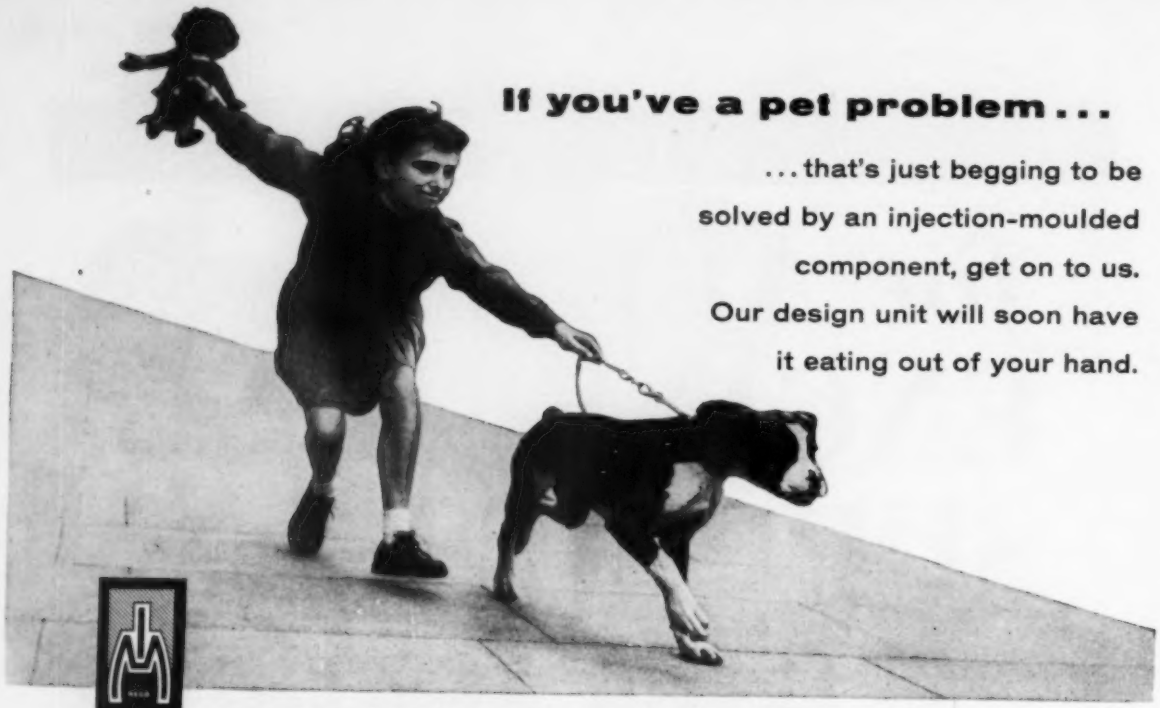

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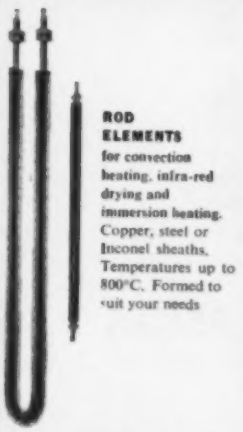

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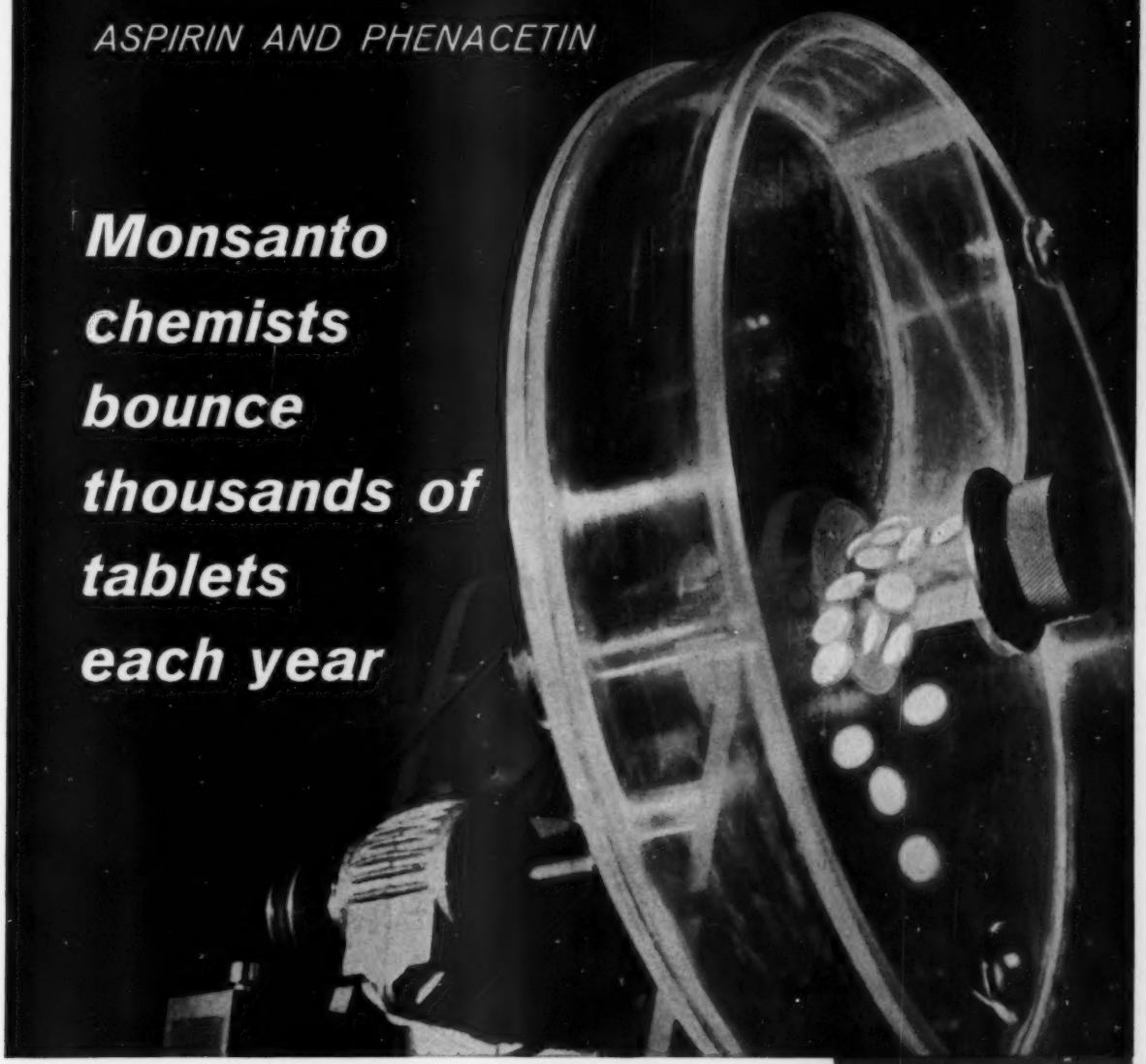

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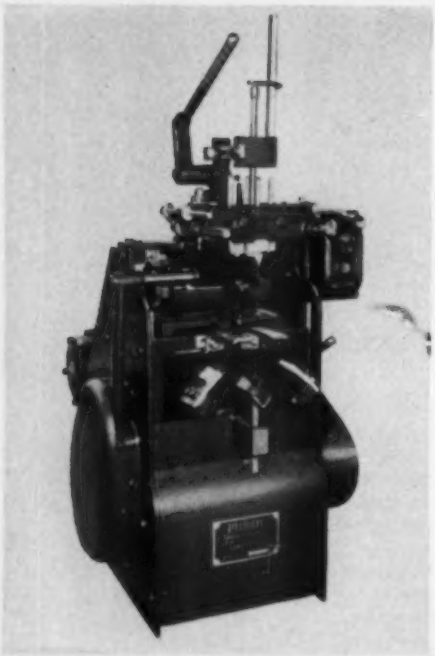

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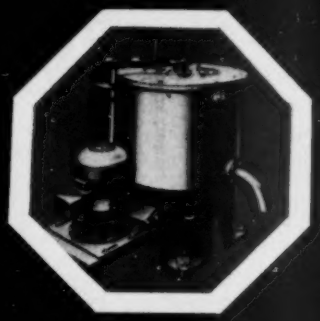

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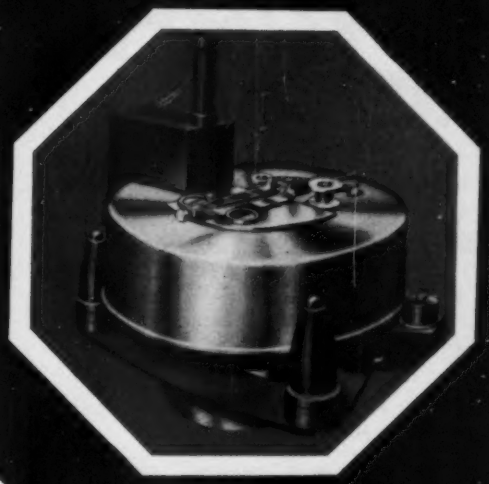

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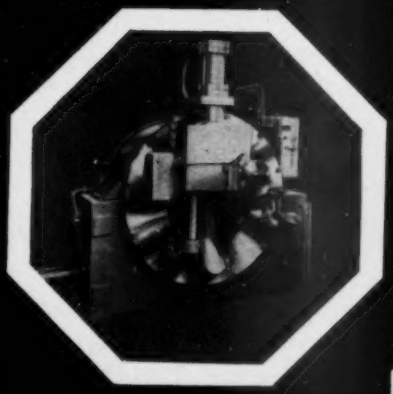

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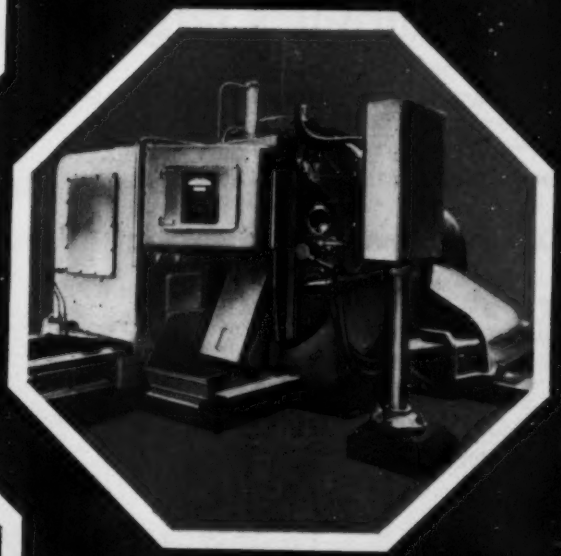

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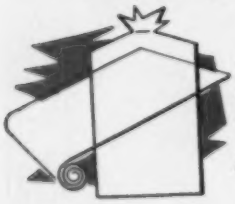

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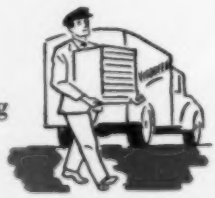

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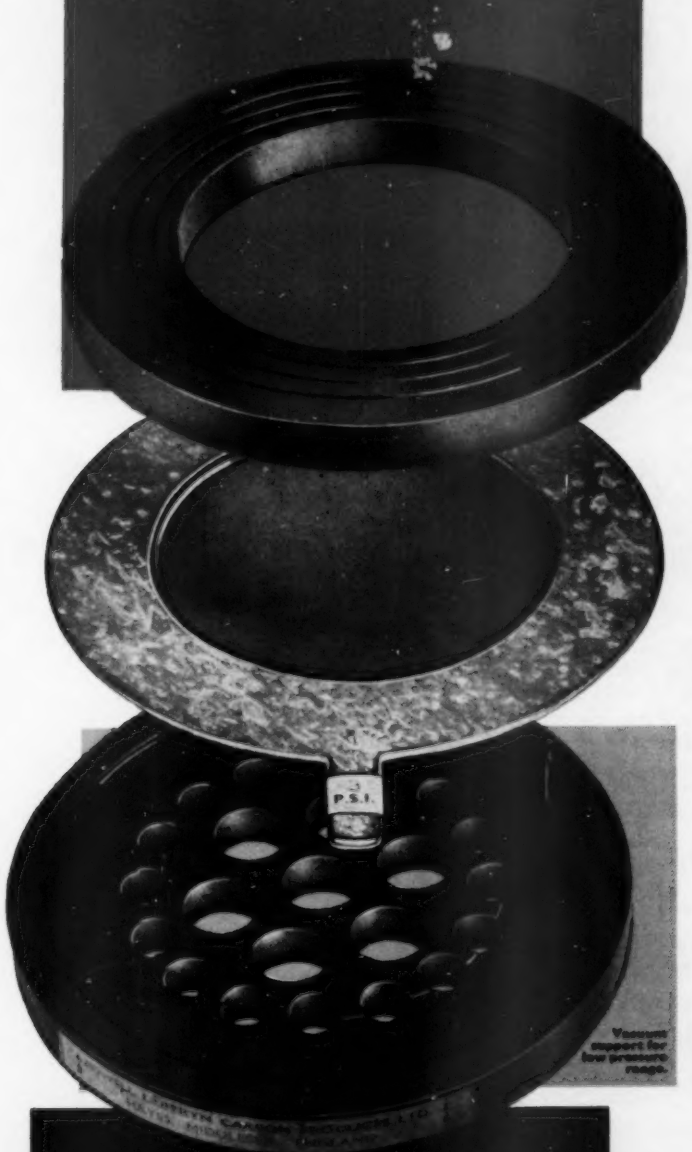


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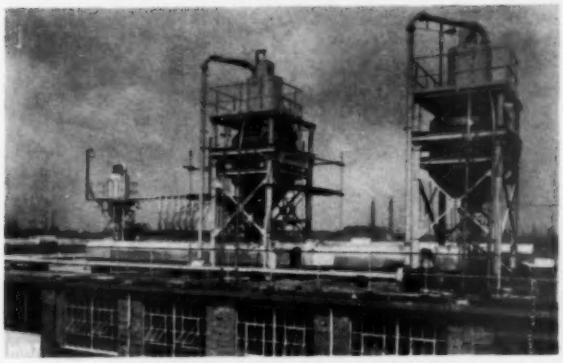

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# *Manufacturing Chemist*

**Editor: W. G. Norris**

Vol. XXXII, No. 8 AUGUST, 1961

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## Onus of proof

STOCKTAKINGS are necessary and salutary and it is no bad thing that there is the Cohen Committee to make a periodical check of the drug list. Some newspapers made a fuss about the latest review which gave an "O" to 247 products "not proved of therapeutic value." Some of these are made by famous firms and the implication was that these firms, many of them heavy spenders on research, have less excuse for scoring "O's" than the small fry. Of course, not proven is not necessarily "guilty." It is very hard to prove a negative. The fact remains that some of the proscribed preparations are still thought to be efficacious by some doctors. Indeed, unless doctors believed they were useful, presumably none of the 247 preparations would still be prescribed.

One loquacious but not particularly qualified critic said in the *Guardian* that the Cohen review exploded the argument that high prices are justified by research, since it appeared that even some of the most famous pharmaceutical firms are unable to distinguish between useful drugs and doubtful ones.

A difficult and interesting question is raised. If a product continues to be in demand, is the manufacturer obliged to test it periodically to see if it fulfils contemporary criteria of therapeutic value, bearing in mind that these criteria are continually changing? The controlled clinical trial has only come into popular use since the war. Presumably many of the newly proscribed products were marketed some years ago before modern testing techniques were developed. Should manufacturers spend their research funds not only on new drugs but on testing old ones too? Or should they be satisfied by the verdict of the market and continue to supply a preparation as long as doctors require it?

## Delusive dummies

THE therapeutic value of suggestion has long been recognised. The "bottle of coloured water" has been laughed to scorn, but how many people have been helped by a daily dose from this now discredited bottle. They firmly believed the placebo "did them good" and probably it did. How otherwise can we explain the "placebo effect" which is bedevilling clinical trials? Many patients are placebo-reactors and improve when given dummy tablets in clinical trials, believing they contain active substances. The placebo effect tends to be most marked in patients suffering mental disturbances and psychosomatic diseases, such as peptic ulcer and asthma; in both groups of diseases suggestion plays a great part.

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This result is astonishing, but it will not surprise clinicians who have studied the placebo effect. For instance, two years ago Dr. Frances Murphy of the University of Belfast reported that two-thirds of a group of angina patients improved considerably after treatment with Tersavid (1-benzyl-2-pivaloylhydrazine). She and her colleagues then conducted another trial, this time "double blind" and randomised so that there was no selection of patients, the drug being given at random and neither the patient nor the doctor knowing whether a placebo or a real drug was being given. The result was that both the placebo and Tersavid gave approximately the same response, between 33 and 35%.

Results like these demonstrate the alarming aberrations that can be caused by placebos in clinical trials. They also imply that many drugs introduced over the years and since discarded were, in fact, useless from the beginning. Now that the dangers of the placebo effect have induced clinicians to adopt strict double blind testing techniques combined with rigid statistical control, the risk of a useless drug being put on the market is minimised. But the disturbing fact remains that placebos are sometimes effective. For instance, H. K. Beecher of Harvard Medical School reports that placebos relieve pathological pain (*Science*, 1960, **132**, 91).

## Activation analysis

CHEMICAL ANALYSIS is taken another step towards the 100% push-button era by the development of activation analysis. High energy, fast neutrons bombard the sample and disarrange the nuclei of some of its atoms. In returning to their normal states these nuclei emit gamma rays which are characteristic for each type of atom. Detection equipment—usually a scintillation counter hooked to a gamma ray spectrometer—can identify each element present by the radiation emitted.

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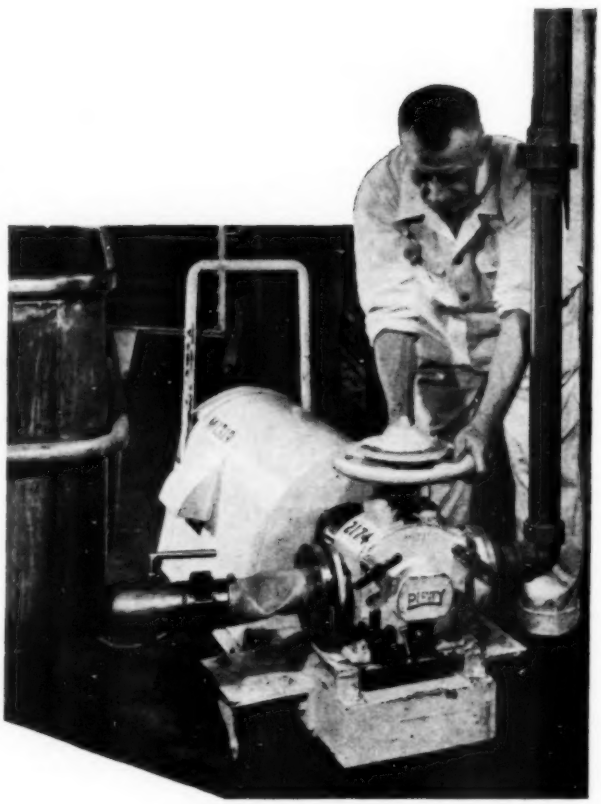

*A 2" bore portable "Easiclean" pump handling dermatological creams at Genatosan Ltd.*

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# Topics and Comments

## Onus of proof

STOCKTAKINGS are necessary and salutary and it is no bad thing that there is the Cohen Committee to make a periodical check of the drug list. Some newspapers made a fuss about the latest review which gave an " O " to 247 products " not proved of therapeutic value." Some of these are made by famous firms and the implication was that these firms, many of them heavy spenders on research, have less excuse for scoring " O's " than the small fry. Of course, not proven is not necessarily " guilty." It is very hard to prove a negative. The fact remains that some of the proscribed preparations are still thought to be efficacious by some doctors. Indeed, unless doctors believed they were useful, presumably none of the 247 preparations would still be prescribed.

One loquacious but not particularly qualified critic said in the *Guardian* that the Cohen review exploded the argument that high prices are justified by research, since it appeared that even some of the most famous pharmaceutical firms are unable to distinguish between useful drugs and doubtful ones.

A difficult and interesting question is raised. If a product continues to be in demand, is the manufacturer obliged to test it periodically to see if it fulfils contemporary criteria of therapeutic value, bearing in mind that these criteria are continually changing? The controlled clinical trial has only come into popular use since the war. Presumably many of the newly proscribed products were marketed some years ago before modern testing techniques were developed. Should manufacturers spend their research funds not only on new drugs but on testing old ones too? Or should they be satisfied by the verdict of the market and continue to supply a preparation as long as doctors require it?

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According to chemists of the Shell Development Co. at Emeryville, California, the new technique enables chemicals to be analysed in a " routine ten

minutes" instead of an hour or more. They have developed procedures for spotting 26 of the elements which occur most frequently in petroleum.

Recently the laboratory has installed a new type of particle accelerator that has made it possible to detect at least nine more elements. This is a deuteron accelerator, a machine that fires deuterons—the positively charged nuclei of heavy hydrogen—at speeds of 8·5 million miles an hour at a target of extra heavy hydrogen or tritium. Under this bombardment the tritium emits high energy neutrons which are used to bombard the samples under study, making them radioactive.

Previous to using the deuteron accelerator to produce neutrons, Emeryville used a Van de Graaff accelerator. However, the Van de Graaff machine is designed mainly to study the effect of high energy radiation upon chemical reactions, and is used at Emeryville to a large extent for such research. Furthermore, the Van de Graaff's high cost and size make it unsuitable for routine analytical work in the average laboratory. The cost of the deuteron accelerator is about 20,000 dollars compared with 140,000 dollars for a new Van de Graaff.

It is believed that Emeryville is the only industrial laboratory to be using semi-automatic activation methods as a matter of routine.

With these methods it is possible to pick out minute quantities of some elements. For example, the technique will detect a single part of vanadium in 10 million parts of oil.

Beyond its present use in research work, Shell sees the equipment as a potential tool in control laboratories at refineries and chemical plants. The radioactivity produced in the samples rapidly disappears. so that samples can be used safely in other tests after they are analysed.

## Ambergris puzzle

THE biochemical synthesis of ambergris is still a mystery, according to Dr. C. P. Idyll of the Marine Laboratory of the University of Miami, who recently published his conclusions in the annual report of the Smithsonian Institute. Ambergris is passed out from the intestine of the sperm whale in the form of unattached lumps of various sizes and it was once valued at more than its weight in gold. Now prices run from 15s. to £3 8s. oz.

The whale is the sole source of ambergris, but there is reason to believe that the squid or cuttlefish eaten by the whale may contribute to the production of ambergris, since the indigestible beaks of these creatures are usually found embedded in the lumps.

Ambergris is found chiefly in temperate latitudes and is dark, sticky and bituminous when it emerges from the whale's intestine. It gradually improves in odour and lightens in colour after floating in the water. The oldest lumps are chalky white and are the most sought after as perfume fixatives.

Some notable finds of ambergris have occurred recently. In 1953 Dr. Robert Clarke, a British scientist, found a chunk weighing 926 lb. This came from a male sperm whale caught in the Antarctic. One chunk weighing 982 lb. was reported by the Dutch East India Co. in 1880.

The Marine Laboratory of the University of Miami has recently issued a bulletin detailing methods for finding and recognising ambergris.

## New members: the S.C.I.'s problem

FOR the first time for several years the decline in the membership of the Society of Chemical Industry has been halted. At the end of 1960 the membership totalled 6,897, an increase of seven over the year. Small as the increase is, it is better than a decline, and it is to be hoped that the Society, now in its 80th year, will continue its upward trend and make good and eventually overtake the losses of the past years.

At the annual general meeting in Oxford last month both the honorary secretary, Dr. Cameron, and the president, Lord Fleck, referred with some concern to the membership situation. Lord Fleck had some positive suggestions for improving matters. Rightly he has seen the problem as one of attracting younger men into the Society. Admittedly there are today many more societies and organisations claiming the allegiance of chemists than there were even 20 years ago. Many are highly specialised, and since everyone is more or less a specialist today they are often preferred to the more general type of society. The S.C.I. has countered this objection by developing its subject groups side by side with its local sections. There are now 13 groups, ranging from agriculture to plastics and from corrosion to microbiology, and yet another—to cover industrial water—is planned. By belonging to a group a member can almost certainly satisfy his specialist interests.

But the decline in membership implies that the rich facilities offered by the S.C.I. are not sufficiently appreciated, particularly by younger men. Lord Fleck, in his presidential address, suggested that students of the new Colleges of Advanced Technology should be the target for a membership campaign. One step he proposes is to offer free subscriptions to *Chemistry and Industry* to each C.A.T. to be given to the most promising students at the discretion of the professors. A total of 54 subscriptions might be required. No one expects that this will dramatically increase membership, but it is a positive suggestion.

The Society might also think about other ways of publicising its activities. For instance, is sufficient use being made of the general and technical press? Without going to the length of employing a public relations officer, the Society could get a great deal of useful publicity merely by ensuring that its activities, including the more important papers it sponsors, are regularly brought to the attention of editors. Much of this material is of first-class interest and its wider publication in extract form would help to project the Society as a virile and progressive

organisation that deserves the much wider support of people in chemical industry.

Besides his idea of free subscriptions for C.A.T. students, Lord Fleck made another interesting suggestion. He recalled that the Society's charter charged it to encourage invention in a broad sense. Under modern conditions he thought this might be interpreted as the sponsoring of investigations of general interest to the chemical and allied industries. For example, the Society might sponsor a study of the changes in the atmosphere caused by industrial activity. Or it might employ statisticians and economists to make a much-needed definition of the chemical industry. The Society would appear to be financially strong enough to undertake investigations of this kind. Will it take up the ideas of its eminent and much-respected president?

## Birds and seed dressings

MODERN chemical seed dressings give important protection against soil diseases and pest attacks. Whatever a minority of anti-chemical agriculturists might argue, the cropping facts about seed dressing benefits are incontrovertible. It is also possible for any farmer to argue that if trespassing wild life eats his dressed seed and suffers he is not responsible. He can indeed argue that the birds that eat his seed are also pests. However, it is pressing logic too far and too fast into the complex equilibria of "Nature" to uphold this latter view entirely. Disturbances to the evolved balance of wild life can be serious. If we kill birds that purloin seed they cannot eat pest insects that attack crops during the growing stage. All too often the control of one "pest" has led a few years later to widespread attacks and damage from another. It can never be certain to be in mankind's interest to use toxic substances when their effects can be indiscriminate. There is, too, the question of humanitarian feelings. The death of birds that consume dressed seed is not speedy; it is undeniably painful.

Most people, including many farmers, will welcome the decision of the Ministry of Agriculture and of the firms with interests in seed dressings to abandon the three most dangerous dressings—dieldrin, aldrin and heptachlor—for spring-sown seed. A study of the deaths that have been occurring, notably in the 1961 spring, has shown that it is these fairly new dressings that present the greatest toxic risk. They will be used as from January 1, 1962, only for autumn-sown or winter-sown cereal seed. This is not only a piece of agreed legislative action—it is also sensible selective use of toxic materials. The principal merit of these dressings is their ability to control wheat bulb fly—but the risk of attack from this pest is far greater with autumn- or winter-sown seed. At the same time there is far less trespassing on seed rows by birds in the autumn and early winter, when the countryside is full of other foods for them. For spring-sown seed, dressings which have been shown to be far less toxic to wild life can be used and these should give as much, or nearly as much, protection.

The Ministry must be congratulated upon reaching this hopeful solution so swiftly. The situation became alarming this spring, which owing to the wet weather was a late one for sowing. By June it has been possible to produce the report of a survey of bird deaths and to have discussed this at a meeting with all interested organisations. By early July action had been taken. The Ministry will continue to survey the situation and next June it should be possible to examine the position again in the light of bird casualties during the 1962 spring sowing period. Naturally, a scientific examination of the evidence and facts cannot have been complete during so short a period—what might be called the trend of limited evidence has had to be the basis of decision. But there will be few people who will not regard this trend as sufficiently definite to justify the restrictions.

## Quality controllers

THE SUCCESSFUL functioning of a process may depend on a large number of routine analyses, and although a first-class analyst is more versatile than any instrument, it is worth considering whether an instrument would do the job better.

In "Quality Measurement in the Chemical Factory," a small booklet published by the Department of Scientific and Industrial Research, a physicist and a physical chemist discuss the use of instruments to control chemical production processes.

The importance of quality control in the chemical factory cannot be over-emphasised. The producer of chemicals has to sell his products to a quality specification which generally sets limits to certain impurities. If the product is outside this specification it may be unsaleable and expensive reprocessing may be necessary. Measurement of the quality of a product at a sufficiently early stage in the process can obviate this kind of occurrence. It also helps the manufacturer to obtain a reputation for consistent product quality, enabling him both to keep ahead of his competitors and to meet the demands for higher quality which the development of new processes and new uses for products continually entail.

A manufacturer who takes the trouble to measure the quality of his product will not only be able to maintain consistent quality but also measurements taken over a period of time will give him a better picture of how his process works, and he will have a better concept of the chemistry of the process which will be invaluable in improving the output of the plant; further, measurement of traces of impurities can point to the way the plant is operating and can, for example, show if and at what rate corrosion by the product is taking place.

The advantage of automatic analysis is that the analyst can be released for more creative work, and that continuous control can be exercised without the delay inherent in human supervision. In this booklet

the emphasis is on instruments of proved worth and relative cheapness with a wide range of applications.

The booklet is divided into four main sections dealing with non-specific measurements, specific analytical instruments, sampling systems and automatic control.

The authors pay special attention to gas chromatography. Process-stream gas chromatography analysers with a simple repetition time of one minute are now becoming available, and, linked with automatic controllers, are already controlling chemical processes.

## Pharmaceutical cosmetics

DRUG therapy dates back at least 4,000 years. Ancient as this may seem, the use of cosmetics predates it by many centuries. The thought that beauty and health might be connected occurred to a few, but it is only recently that medicine and cosmetics have been joined in pharmaceutical cosmetics.

Most of the so-called beautifying agents of earlier centuries were so deadly that they caused more harm than good. Water from arsenic springs, quicksilver, belladonna, chalk and white lead all evoked their inevitable penalties. It was not until the birth of antibiotics, hormone therapy and the new vitamin discoveries that a few far-sighted pharmacists and cosmeticians began to see a new horizon.

In Elizabethan England a teenager suffering from internally-caused acne was painted with powdered sulphur and turpentine for an hour, then anointed with butter. Today several dermatological preparations would be available and their active ingredients would include neomycin, bacitracin, gramicidin, tyrothricin, hydrocortisone, pantothenylol and bactericides such as quaternary ammonium compounds, actamer and hexachlorophene. These are rapidly replacing the old standard medicaments: coal tar additives, essential oils and balsams and chemicals such as sulphur, $\beta$-naphthol, resorcinol, zinc oxide, benzoic and salicylic acids. A new antibiotic to treat acne is Declomycin (7-chloro-6-dimethyltetracycline).

Vitamins have also found their way into cosmetics, vitamin A being particularly popular. Although a number of skin and scalp problems can be traced to vitamin or mineral deficiency, the case for external application of the missing elements is still somewhat clouded.

Hormones have had a great impact upon this combined industry, particularly in the treatment of geriatric skin problems. The theoretical basis for the use of hormone creams is the fact that the level of œstrogenic hormones in the body decreases with the advent of middle age, thus contributing to skin aging. Again, there is still much work being done in this field.

There are many other pharmaceutical cosmetics, either in actual use or under consideration. Allantoin in hand creams and lotions helps to promote healing. An array of germicides and bactericides, such as the popular hexachlorophene, now add the pharmaceutical touch to toilet soaps and cosmetic washes. Other such ingredients include new anti-allergy materials; improved sun-screening agents; silicones that protect the skin against dryness, eczema and infection; acetylated lanolins and acetylated cholesterols that help soften the skin; special deodorants to offset the odours of babyhood and malonic acid to inhibit enzymes which stimulate perspiration.

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It seems logical that any product designed to beautify the body should also promote a healthy body; beauty is closely related to physical fitness. Pharmaceutical cosmetics will become increasingly popular as science continues to develop and adapt new materials suited to their use.

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**Fig. 1. Intranasal inoculation of a volunteer with drops of fluid containing a cold virus strain.**

*Reproduced from The Salisbury Times.*

# *COMMON COLD RESEARCH and the OUTLOOK for a VACCINE*

**By D. Taylor-Robinson,* M.D.**

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THE Common Cold Research Unit was established in 1946 under the auspices of the Medical Research Council to study various aspects of the common cold with the aid of human volunteers. Even before the inception of the unit the weight of evidence was that chimpanzees were the only animals susceptible to the common cold apart from human beings; the non-susceptibility of other species was fully substantiated. Chimpanzees, however, were not considered suitable for this sort of research because of their expense and general inconvenience. Over the past 15 years nearly 7,000 volunteers have passed through the unit. Throughout the year, men and women of 18-50 years of age come to the unit for periods of 10 days. They are isolated in pairs or in threes and observed for the first four days to ensure that they are not incubating a cold. On the fifth day the volunteers are inoculated intranasally (Fig. 1) with test or control material and each day thereafter they are observed for signs and questioned for symptoms of a cold. The observations are made " blind "—that is, they are made by a clinician who is unaware of the nature of the material inoculated, whether it be test or control fluid. Although much information on epidemiological[1] and clinical[2] aspects of the common cold and indeed on the virus or viruses (approximate size, stability, etc.) was gained from the use of volunteers alone, it was felt that no major advance could be made without the isolation and growth of the agent or agents in tissue cultures within the laboratory.

* World Health Organisation International Reference Centre for Respiratory Virus Diseases and Common Cold Research Unit, Harvard Hospital, Coombe Road, Salisbury, Wilts.

### Virus propagation

A great stimulus to the study of viruses generally was the discovery by Enders, Weller and Robbins[3] that poliomyelitis virus could be propagated in cultures of cells of non-nervous origin. At this unit, numerous unsuccessful attempts were made to isolate in tissue culture virus from the nasal washings of volunteers. However, in 1953 Andrewes, Chaproniere, Gompels, Pereira and Roden[4] reported that a virus had been propagated in series through 10 cultures of human embryonic lung, colds being induced in volunteers by materials from the fourth, sixth, seventh, ninth and tenth cultures in the series. Unfortunately, however, later passage material did not produce colds, possibly due to loss or attenuation of the strain, and degeneration of the cells in the cultures (cytopathic effect) was never seen. Further, numerous attempts to repeat these results met with no success even though a variety of factors were varied. Then in 1958 culture techniques were altered so that human embryo kidney was used instead of lung and the cultures were maintained at 33°C. instead of 37°C. following inoculation with nasal washings.

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**By D. Taylor-Robinson,* M.D.**

*A common cold is an infection of the upper respiratory passages caused by a virus. The symptoms last about two to three days and consist of watery nasal discharge and stuffiness and sometimes sore throat and cough usually without fever. However, if secondary bacterial infection supervenes, fever, purulent nasal discharge and other complications may arise. Bacteria are known not to be the prime ætiological agents, since bacterial-free filtrates of nasal discharges obtained from subjects with colds are able to produce colds when given intranasally to normal individuals. Adenoviruses and ECHO viruses are associated with much more severe infections of the respiratory tract than a common cold. Occasionally, however, some of these viruses have caused symptoms of a severe cold, but they are not considered to be the ætiological agents of the vast majority of typical common colds. The first part of this article deals with the chronological progress of common cold research that has culminated in the isolation and growth in the laboratory of viruses from subjects with colds. Against this background, the second part deals with the outlook for a common cold vaccine.*

THE Common Cold Research Unit was established in 1946 under the auspices of the Medical Research Council to study various aspects of the common cold with the aid of human volunteers. Even before the inception of the unit the weight of evidence was that chimpanzees were the only animals susceptible to the common cold apart from human beings; the non-susceptibility of other species was fully substantiated. Chimpanzees, however, were not considered suitable for this sort of research because of their expense and general inconvenience. Over the past 15 years nearly 7,000 volunteers have passed through the unit. Throughout the year, men and women of 18-50 years of age come to the unit for periods of 10 days. They are isolated in pairs or in threes and observed for the first four days to ensure that they are not incubating a cold. On the fifth day the volunteers are inoculated intranasally (Fig. 1) with test or control material and each day thereafter they are observed for signs and questioned for symptoms of a cold. The observations are made " blind "—that is, they are made by a clinician who is unaware of the nature of the material inoculated, whether it be test or control fluid. Although much information on epidemiological[1] and clinical[2] aspects of the common cold and indeed on the virus or viruses (approximate size, stability, etc.) was gained from the use of volunteers alone, it was felt that no major advance could be made without the isolation and growth of the agent or agents in tissue cultures within the laboratory.

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### Virus propagation

A great stimulus to the study of viruses generally was the discovery by Enders, Weller and Robbins[3] that poliomyelitis virus could be propagated in cultures of cells of non-nervous origin. At this unit, numerous unsuccessful attempts were made to isolate in tissue culture virus from the nasal washings of volunteers. However, in 1953 Andrewes, Chaproniere, Gompels, Pereira and Roden[4] reported that a virus had been propagated in series through 10 cultures of human embryonic lung, colds being induced in volunteers by materials from the fourth, sixth, seventh, ninth and tenth cultures in the series. Unfortunately, however, later passage material did not produce colds, possibly due to loss or attenuation of the strain, and degeneration of the cells in the cultures (cytopathic effect) was never seen. Further, numerous attempts to repeat these results met with no success even though a variety of factors were varied. Then in 1958 culture techniques were altered so that human embryo kidney was used instead of lung and the cultures were maintained at 33°C. instead of 37°C. following inoculation with nasal washings.

This change in technique produced promising results; although a cytopathic effect was not noted at first in tissue cultures inoculated with nasal washings, the fluids from such cultures produced colds in volunteers.[6] Then in 1959[8] it was found that cultures that had been treated with cold virus (nasal washing) had a greatly reduced ability to support the growth of ECHO 11 virus—the interference phenomenon. Thus, although a cytopathic effect had still not been demonstrated, here at last was a way of demonstrating the presence of a cold virus without the need for volunteers; it was shown further that 33°C. was the optimal temperature for virus growth and that colds that were produced in volunteers by serial passage material were due to virus that had multiplied and not to the persistence of virus from the original inoculum.

Then a fortunate development occurred. A particular batch of medium 199 (a synthetic medium containing amino acids, vitamins and salts) used to grow and maintain the cultures was found to be toxic, since the cells degenerated rapidly before the addition of a virus-containing nasal washing. Fresh supplies of medium were used and found to be satisfactory; furthermore, for the first time, cytopathic changes were noticed in the human embryo kidney cultures inoculated with washings; these came from a subject H.G.P. Analysis of the successful batch of medium revealed that it had a lower sodium bicarbonate concentration and therefore a lower *p*H than that usually used; the lower *p*H proved to be of particular importance. Other experiments demonstrated that the H.G.P. strain of virus would also grow in monkey kidney cells. The extent of the cytopathic effect was increased by using secondary rather than primary cultures (secondary cultures are obtained by dispersing the cells of a primary culture with trypsin and inoculating them into a fresh culture tube), by using 0·03% rather than 0·1% sodium bicarbonate in the medium, 33°C. rather than 37°C. and rolled rather than stationary cultures.[7] Thus the major barrier had been overcome; it was possible to cultivate certain cold viruses within the laboratory and recognise their presence easily without constant recourse to volunteers.

**Tissue culture of viruses**

Perhaps somewhere in the region of 25-50% of the viruses responsible for the common cold syndrome can be grown in tissue culture with the present techniques. For those viruses that could be grown, relatively rapid advances were now possible, for experiments could be carried out in tissue cultures in a few days that might take months to complete in volunteers. It must be pointed out, however, that the need for volunteers has in no way diminished; on the contrary, the necessity of testing firstly the different strains of virus isolated in tissue culture in the natural host, and secondly those viruses that are not cultivable as well as studies on the antibody response, have increased the need for volunteers.

Once the initial break-through had been made, a number of different strains of virus were isolated in human embryo kidney cells from different subjects in various outbreaks of colds. It soon became clear that these virus strains fell into two groups: (i) those capable of propagation within human embryo kidney cells only, and (ii) those that could be grown in monkey kidney cultures as well. These findings were confirmed in Sheffield by Hobson and Schild,[8] who also reported that the H.G.P. strain of virus would grow in a continuous line of human laryngeal carcinoma cells known as H.Ep-2.

As might be expected, because human embryo kidney tissue is much less readily available than monkey kidney, most of the work so far at this unit has been carried out on those strains that grow in the latter—the so-called "M" strains. Thus an important aspect has been the development of a method of assay for these strains by Parsons and Tyrrell[9] derived from the original work of Dulbecco.[10] He showed that when a monolayer of chicken embryo fibroblasts was infected with the virus of Western Equine Encephalomyelitis and then covered with a layer of agar, incubation at 37°C. for a few days resulted in the appearance of circular clear areas or plaques. These plaques were observable by the naked eye and consisted of an area of degenerating and dead cells caused by virus infection. The agar served to localise the infective process and prevented widespread involvement of cells in the monolayer. Of more importance, he showed that one plaque was produced by one infectious unit, since there was a direct proportionality between the number of plaques and the virus concentration.

**Virus assay**

The assay developed for those cold viruses growing in monkey kidney cells differs in that it is a microplaque technique performed in the following way. Sheets of cells are grown in test-tubes, the virus inoculum added and the cultures rolled at 33°C.; after two to three days focal areas of degeneration appear (Fig. 2) and these foci or microplaques are counted, using the low power of the microscope. Here again the number of microplaques is directly proportional to the concentration of the virus inoculum. An agar overlay is not used since this suppresses the formation of microplaques, possibly as a result of the decreased oxygen supply; consequently

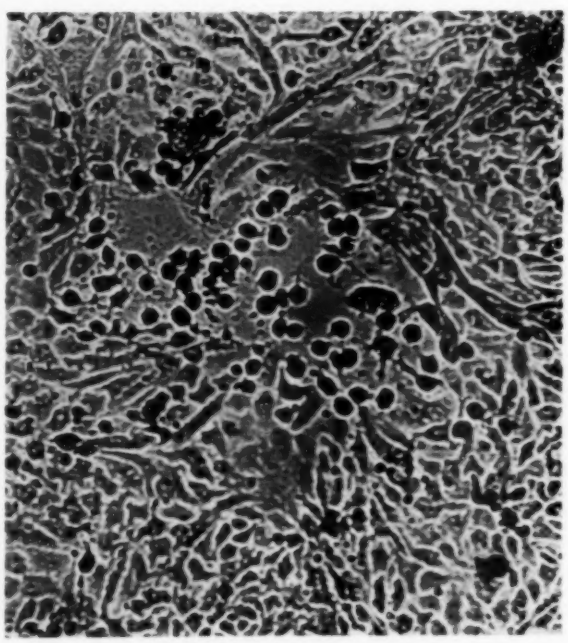

**Fig. 2. A focus of degenerated cells or microplaque two days after the inoculation of a monkey kidney culture with B632 virus. Magnification ×118.**

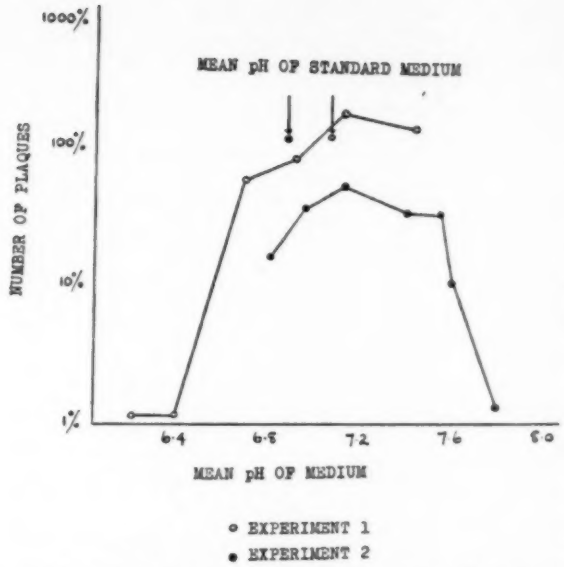


**Fig. 3. The number of plaques developing in tissue cultures containing media buffered with phosphate at various *p*Hs—expressed as a % of the number of plaques in cultures containing the standard amount of sodium bicarbonate (0·03%).**

*From Parsons and Tyrrell, "Nature" (Lond.), 1961, 189, 640.*

secondary plaques do occur, but provided that plaques are counted within three days of virus inoculation the counts follow a Poissonian distribution. The method is, therefore, a fairly precise and simple way of assaying virus. Moreover, it was discovered that the conditions previously found necessary for virus isolation were also essential for the appearance of the maximal number of microplaques. Thus the temperature was found to affect the plaque count as can be seen from Table 1.

**Table 1. The Effect of the Temperature of Incubation on the Number of Microplaques**

| *Day of reading* | *Plaque count on cultures incubated at* | | |
|---|---|---|---|
| | *30°* | *33°* | *36°* |
| Day 2 .. .. | 12 | 1,200 | 190 |
| Day 3 .. .. | 1,400 | 14,000 | 150 |

From Parsons and Tyrrell, *Nature* (Lond.), 1961, **189,** 640.

It was also possible to determine more precisely whether the low concentration of bicarbonate was important in itself or whether the low *p*H was the important factor; parallel cultures, each inoculated with the same amount of virus, were maintained either in media containing various concentrations of sodium bicarbonate or sodium phosphate. The *p*H of the medium was measured and the number of plaques that appeared was counted in each case. As seen from Fig. 3 the plaque count is affected by the *p*H of the medium rather than by the concentration of bicarbonate within it.

## Feasibility of vaccine

So far, I have tried to give some idea of the development of research on the common cold as a background to the problem of producing a vaccine. There are two factors to consider in assessing whether a vaccine is a feasible proposition. Firstly, whether antibodies are produced in response to a cold (the host response), and if so whether such antibodies are able to protect against a further attack; secondly, the number of different types of virus that may be encountered and therefore the number of types that need to be combined for the production of an effective vaccine.

## The host response

The presence of neutralising antibodies in sera and a quantitative measurement of their concentration has been carried out by means of neutralisation tests. The general laws of the kinetic neutralisation test were first propounded by Burnet, Keogh and Lush[11] and extended by Dulbecco to viruses forming plaques under agar. Dulbecco, Vogt and Strickland[12] showed with poliomyelitis virus that when different concentrations of immune serum were added to the same amount of virus, the rate of virus disappearance (the slope of the lines in Fig. 4) was directly proportional to the antibody concentration. The logarithm of the percentage of original virus that remained active was inversely proportional to the time of incubation ($t$) and to the concentration of antibody (C). This may be expressed as follows:

$$\log e \frac{Vo}{Vt} \propto tC$$

or

$$\log e \frac{Vo}{Vt} = KtC$$

where "K" is a value that is proportional to the rate of inactivation and is constant for a given virus and a given serum. A serum that has a high K value contains a high concentration of antibody and the slope of the inactivation curve is steep. Further, since the curves in Fig. 4 pass through the point of origin the reaction is of first order type, which suggests that the neutralisation of a virus particle is due to a single event—the combination of a molecule of antibody with a critical site on the virus.

In general, the principles outlined above apply to the neutralisation of common cold viruses by immune sera and it has been possible to study the host antibody response by means of a kinetic neutralisation test in conjunction with the microplaque assay technique. The test is carried out by mixing virus and serum together and incubating the mixture for 2 hr. at 22°-25°C.; the mixture is then inoculated into monkey kidney cultures and the microplaques are counted after the cultures have rolled at 33°C. for two to three days. An example of such a test is shown in Table 2. The numbers of plaques counted in the presence or absence of serum are used as Vt and Vo in the equation presented above and the K value of the serum is thus calculated. By such means it has been possible to demonstrate a rise in serum antibody following a natural or experimentally produced

**Table 2. Total Plaque Counts after Three Days in each Group of Five Monkey Kidney Cultures inoculated with the Following Mixtures**

| *Virus + Medium* | *Virus + Normal Serum** | *Virus + Immune Serum** | *% Reduction in count* | *K Value for immune serum* |
|---|---|---|---|---|
| 69 | 63 | 7 | 90 | 0·37 |

* Dilution = 1/20.

cold. Fig. 5 shows that the serum obtained at the same time as the intranasal inoculation of virus did not contain neutralising antibody, but serum obtained 14 days later possessed antibody.

At the moment information concerning the persistence of neutralising antibody at a high level after a cold is limited; however, subject H.G.P. still has a significant level of neutralising antibody three years after the original infection.[13] This would suggest that the high incidence of colds in the population, probably about two to seven per person per year, is due to the existence of a number of different antigenic types rather than to the short duration of immunity.

**Does neutralising antibody protect ?**

Although we have been able to show that neutralising antibody is elicited in response to a cold, there remains the important question of whether such antibody really protects. In America, Jackson and Dowling[14] reported observations on five strains of colds obtained in different years. They inoculated volunteers with the nasal washings of one or another of the five strains. On re-inoculation some months later, the volunteers proved resistant to the same strain, but were susceptible to any of the other 4. These observations not only support the belief that immunity persists, but also show that there are a number of antigenic types of cold virus. The most recent and convincing volunteer experiment supported by laboratory studies on the effectiveness of antibody in protecting against colds has been carried out by Bynoe, Hobson, Horner, Kipps, Schild and Tyrrell.[15]

Volunteers were inoculated intranasally with H.G.P. virus and bled at the same time and bled again 14 days later, irrespective of whether they developed colds or not. In general, it was found that those volunteers who did develop colds had a low level of antibody in the pre-inoculation serum and a high antibody level 14 days later; those who did not develop colds had an initial high concentration of antibody in their sera. This indeed suggests that neutralising antibody protects and that a vaccine might be useful. In the experiment described, however, the serum of those subjects who did not develop colds contained antibody that had been stimulated quite obviously by natural infection. It still remains to be seen whether a vaccine, given perhaps intramuscularly, is able to stimulate the production of sufficient antibody to be of protective value.

**The different types of common cold viruses**

An effective vaccine must contain the different virus types that are prevalent in the community. More than 30 strains of virus have been isolated in human embryo kidney (" H " strains) and there are a further nine strains that will grow in monkey kidney cultures as well (" M " strains). The typing of these various strains is a slow task and is being carried out by means of the neutralisation test already described. The following examples give some idea of the ways in which the " M " strains are being sorted out.

If two identical strains of virus are set up in a neutralisation test against the same serum, then the results, whether expressed as K values or purely as percentage plaque reduction, should be the same. It can be seen from Table 3 that when H.G.P. and B632 strains of virus were set up in the same test against the same series of normal young adult sera, the results in no way paralleled one another; although some sera contained antibody to

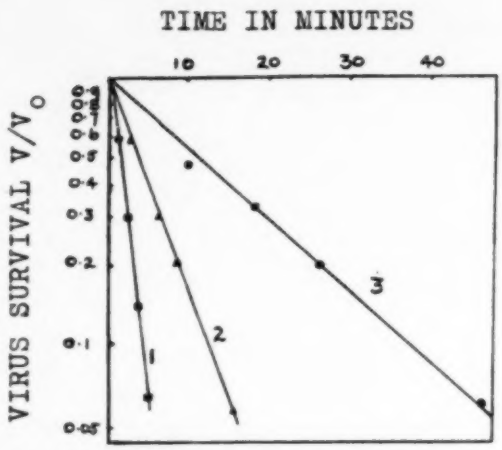


**Fig. 4. Neutralisation of poliomyelitis virus using serum concentrations in a ratio of 10/3·3/1 for curves 1, 2 and 3.**

*From Dulbecco et al., " Virology," 1956, 2, 162.*

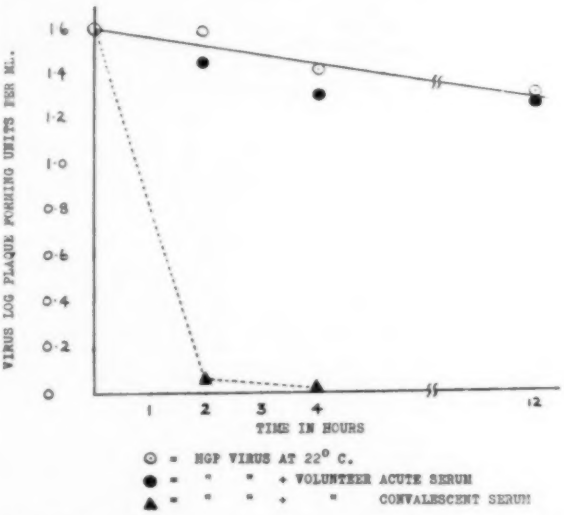


**Fig. 5. Demonstration of rise in neutralising antibody in experimentally produced cold as shown by virus neutralisation with convalescent serum.**

**Table 3. Antibody to HGP and B632 Virus Strains in Young Adult Sera**

| *Sera* | *Antibody to HGP* | *B632* |
|---|---|---|
| 1 | — | + |
| 2 | — | + |
| 3 | + | + |
| 4 | + | + |
| 5 | + | + |
| 6 | + | — |
| 7 | — | — |
| 8 | + | + |
| 9 | — | + |

+ = More than 50% plaque reduction and indicates presence of antibody at a 1/20 serum dilution.

both viruses and some no antibody at all, other sera contained antibody to H.G.P. virus only and yet others only antibody to the B632 virus strain. This suggests that H.G.P. and B632 are different.

The preparation of immune sera in rabbits to each of the isolated virus strains is a slow process, since the viruses grow only to a low concentration in tissue culture ($10^3$-$10^4$ plaque-forming units/ml.) and therefore numerous rabbit inoculations are necessary before useful sera are obtained. However, immune sera have been prepared to some of the strains. Thus an immune serum to H.G.P. virus does not neutralise the B632 strain, although of course it does neutralise the homologous virus. Conversely, B632 antiserum neutralises B632 virus but not the H.G.P. strain. This again demonstrates the distinction between these two strains. Furthermore, the use of even a single immune serum in the kinetic neutralisation test may give valuable information; when the same serum is used with two different strains of virus, the difference between the " K " values may be an expression of the difference between the two agents.

The evidence obtained from such experiments leads us to believe that there are several serotypes among the " M " strains of virus. On the other hand, typing of the " H " strains has only just begun because of the lack of tissue culture material necessary for experiments with these strains. Even at this early stage, however, there is a hint that, here too, there are several different strains.

In conclusion, it appears that there are several distinct serological virus types; further research on the lines indicated will reveal their number. The more serotypes encountered, the more difficult is the task of producing an effective vaccine. The H.G.P. virus strain was isolated from nasal washings obtained in 1957; a virus of this sort has not been isolated since this time. The possibility that common cold viruses may recur in cycles as the immunity of the population wanes is an interesting speculation. If this be so, a vaccine prepared with a limited number of virus types prevalent in the community over a certain period of time could be an effective preventive measure over this duration of time. Evidence suggests that immunity may be due to high serum neutralising antibody levels; however, even if in principle a vaccine could be produced, it still remains to be seen whether a vaccine containing a single antigenic virus type is effective in producing immunity against the virus which it contains.

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**Capsule developments.** The first issue of a quarterly news-sheet entitled *Capsule News* has been published by R. P. Scherer Ltd., Slough, Bucks, to provide information on Scherer's latest developments in research, new manufacturing processes, etc. Although full attention will be paid to the gelatin capsule's achievements and possibilities in the pharmaceutical industry, the news-sheet will cover developments in new fields.

# Practical Progress in Distillation

## *PACKED COLUMNS . . . MOLECULAR STILLS*

**By K. E. Porter,* B.SC.**

*Distillation devices for fine chemicals, pharmaceuticals and essential oils must possess special qualities. The quantity of material dealt with is relatively small, the separating power required is often large, and the materials are frequently heat-sensitive and require distillation at reduced pressures. Thus the bubble plate columns of the heavy chemical industry are usually unsuitable. In this review, which is concerned only with distillation in packed columns and molecular stills, Mr. Porter considers recent work under two headings: 1. Work on fundamentals, the object of which is to enable the designer to predict the type and size of equipment best suited for a particular separation and throughput. 2. The invention of new distillation devices with an improved performance for certain duties.*

### PACKED COLUMNS

#### Fundamentals

THE first requirement in the design of any distillation column is knowledge of the vapour-liquid equilibria for the system to be separated. In the distillation of essential oils containing different types of hydrocarbon compounds and oxygenated derivatives such as aldehydes, alcohols, ketones, acids, etc., the resulting mixture will be non-ideal and the equilibrium ratio or relative volatility will depend not only on vapour pressures but also on activity coefficients. Thus the correct relative volatility will differ from that calculated from boiling-point differences. Only limited success has so far been achieved in the prediction of activity coefficients. One recent method[1] used Hildebrand's solubility parameter calculated approximately from heats of vaporisation to give an improved method of prediction for binary systems of hydrocarbons and hydrocarbon derivatives. Progress has been made in correlating binary and ternary system data by thermodynamical methods. The effect of temperature and pressure may be predicted. The methods available are reviewed by Ellis and Bourne.[2]

It seems unlikely that a generally applicable method of predicting vapour liquid equilibria which takes into account non-idealities in the liquid (activity coefficients) will be available for some time.

The prediction of packing efficiency or H.E.T.P. from the physical properties of the system to be separated and from properties of the packing has continued to receive attention. Two new methods have been published for the prediction of H.E.T.P. for normal systems. Other workers have explained the abnormally low separation efficiencies which are sometimes obtained in terms of system properties.

Leva in his book on packed columns[3] gives three methods of predicting H.E.T.P. and gives an example showing a large difference between the different methods. The method recently proposed by Morris[4] is an extension of the methods developed in a previous work on the design of absorption towers.[5] This method assesses separately the effect of the turbulence in the gas and liquid phases on the rate of mass transfer in different types of packing. The method is as yet restricted to traditional packings (rings and saddles) for which data is available. The probably incorrect assumption is made that the extent of the wetted area of a packing is independent of the physical properties of the liquid. However, Morris compared his predictions with experimental data for several different systems and obtained good agreement. An empirical method of H.E.T.P. estimation has been developed by Cornell *et al.*[6] based on experimental data from 20 previous works. The difference between predicted H.E.T.P. and experimental varied from 5% to 100%. The variables include the height and diameter of the column. These are omitted in classical packed column theory which assumes the phases to be uniformly distributed across the column cross-section, although it has long been known that channelling of liquid and wall flow often occur. A paper by Mullin[7] discusses the effect of a fixed amount of maldistribution in a packing when it separates different systems. Under certain conditions "pinch" zones of reduced or zero mass transfer can develop. This explanation was used by Norman[8] to account for the abnormally low efficiencies found in the separation by distillation of aniline and water in a packed column (Fig. 1). Maldistribution is found to be most serious when the ratio $m\frac{G}{L}$ is high, or when a large number of theoretical plates are required for a separation. In these cases great care should be taken in designing the liquid distributor since the separation obtained may depend more on the absence of maldistribution than on any other factor.

**Nomenclature**

| | |
|---|---|
| H.E.T.P. | Height of packing equivalent to one theoretical plate. |
| $m$ | Slope of equilibrium line. |
| L/G | Slope of operating line. |

The importance of wetting the packing has been recognised for many years, and its absence is used to explain the fall-off in efficiency of a packing which is insufficiently irrigated at low liquid rates. Recently attention has been given to the effect of mass transfer on the stability of the liquid film. It has been shown that if the composition changes in the column are such that the surface tension of the liquid at

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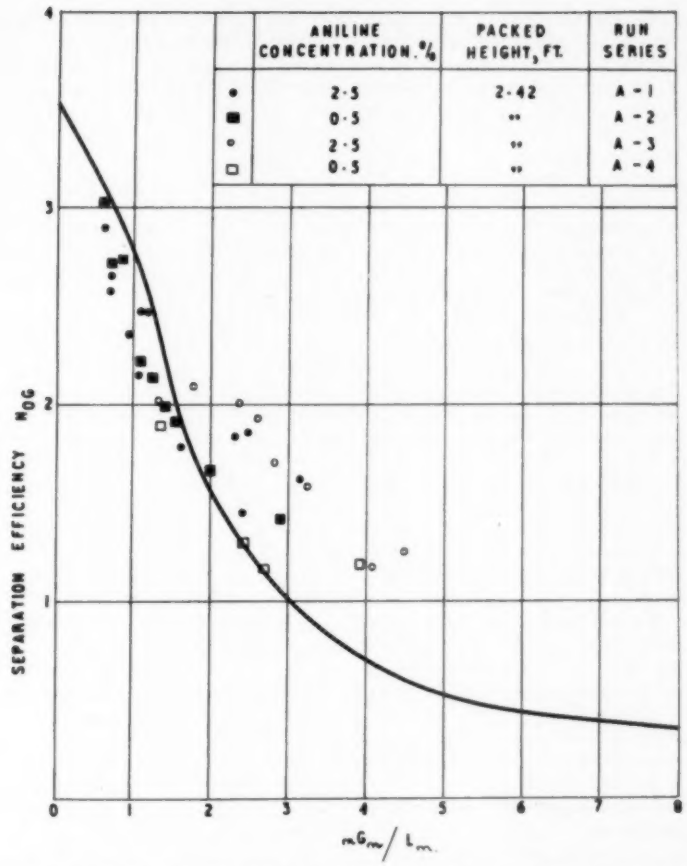


**Fig. 1. The effect of maldistribution on the efficiency of a packed column distilling an aniline-water mixture. High values of H.E.T.P. can be expected when $m\frac{G_m}{L_m} > 1{\cdot}0$. (See W. S. Norman, ref. 8.)**

the top of the column is greater than that of the liquid at the bottom of the column, the liquid film on the packing tends to break up and form separate streams. This causes a decrease in interfacial area and results in a loss in efficiency. The occurrence of this Maragnoni[9] effect in distillation columns has been investigated extensively by Zuiderweg,[10] who introduced the nomenclature Positive systems (liquid surface tension greater at the bottom of the column) and Negative systems (liquid surface tension greater at the top of the column). Systems with little surface tension change were called Neutral systems. Normal values of H.E.T.P. are obtained for the distillation of Positive and Neutral systems. Negative systems, however, frequently require an abnormally large height of packing for each theoretical plate.

## Developments in packing materials

A history of packing materials would reveal an extraordinary variety in the things that have been poured into columns to achieve separations by distillation. An early worker in the field, Fenske,[11] reports the results of tests on chain, nails, rivets and wire. Many commercial separations need relatively few (say less than ten) theoretical stages, and where pressure drop is not very important these may be achieved with Raschig rings. An H.E.T.P. of the order of 8 to 9 in. may be obtained with ½ in. Raschig rings. If a slightly higher efficiency is required Intalox saddles may be used. The efficiencies of Raschig rings and saddles have been compared by Field.[12] In the past high efficiency packing has been restricted mainly to analytical columns to fractionate a low throughput of material to a high degree of purity. Perhaps the main incentive for the development of high efficiency packing for use in large columns has been the post-war interest in isotope separations. These separations are difficult and if obtained by distillation usually require columns with 100 theoretical plates or more. It is not uncommon nowadays for columns of a foot in diameter to be packed with high efficiency low pressure drop packing. The packing is usually made of stainless steel or Monel metal wire and is thus expensive, making the correct choice of the type and quantity of packing essential.

A review of all types of tower packings for both the fine and heavy chemical industry has been made by Randall.[13] Ellis and Varjavandi[14] have reviewed high efficiency packings. These authors compare packings on the basis of pressure drop per theoretical stage. This is an important criterion in choosing a packing for the distillation of heat-sensitive materials. High efficiency packings are designed for complete wetting of the available surface area. Greenaway[15] has shown experimentally that only a small proportion of the total liquid wets the inside of Raschig rings. Thus to increase the efficiency of a ring type packing the wall of the ring must be made permeable to liquid. This is probably the explanation of the increased efficiency of the Pall ring which has rectangular holes let into the side of the ring. In metal these can be made as small as ½ in. and thus are suitable for 6 in. diameter columns.

High efficiencies have been obtained by means of rings made from wire gauze. The first of these, the Dixon ring,[16] is made of a single layer of gauze. The H.E.T.P. of ⅛ in. dia. rings may be as low as 1 in. rising to 3 to 4 in. for ½ in. rings. The pressure drop is lower and the throughput higher for the larger rings. The high efficiency of Dixon rings is only obtained after pre-flooding the packing, which in some circumstances may be a serious disadvantage. For instance, the extremely high pressure drop through the packing during the pre-flooding operation raises the temperature of the still with the consequent risk to heat-sensitive materials, also a larger heat supply for the still must be available.

Borad rings are a development of the Dixon ring. Developed by the

British Oxygen Co., the rings are made of two layers of wire mesh instead of one. This promotes spread of the liquid reflux by capillary action between the gauze layers with the object of obtaining full efficiency without pre-flooding. The results of recent tests by Ellis and Goodwin have shown that this has been achieved for the smaller rings (¼ in. rings in 3 in. dia. column), but as the column size and ring size increase, pre-flooding is still needed to reach maximum efficiency.

The trend in packing development is to provide a structure of high interfacial area and high voidage which is self wetting, usually by capillary action along wires. These requirements have been met most successfully by Multifill packing, first described by Bragg.[17] This packing is a knitted fabric of multifilament wire strands. The fabric is crimped and rolled into cartridges to fit the column. The crimping keeps adjacent layers apart and provides the high voidage. No pre-flooding is needed with this packing which is truly self wetting along the multifilament wires. This was demonstrated by Varjavandi,[18] who found that pre-flooding not only increased the efficiency of ¼ in. ceramic Raschig rings, but also increased the holdup and pressure drop. With Multifill packing, however, pre-flooding had no effect on efficiency, pressure drop or holdup. Ellis and Varjavandi have shown[14] that a lower pressure drop per theoretical stage is obtained with this packing than with any other, and Ellis[19] reports the results of tests on the distillation of lemon oil with Multifill packing at 1-3 mm. pressure. The drop between the distillate and still temperatures ranged from 10°C. to 25°C., increasing as the distillation proceeded. The distillate fractions contained no aldehydes, all the aldehydes being concentrated in the 15% residue. The high efficiency of Multifill packed columns has been found to fall as the column diameter increased.[17] Work (to be published) at the University of Birmingham has shown that a rearrangement of the knitted mesh allows the high efficiency to be maintained.

## MOLECULAR DISTILLATION

The term molecular distillation is generally applied to unobstructed path distillation carried out at a residual gas pressure of 1 micron or less, where the mean free path of the residual gas molecules is greater than the width of the distilling gap. Molecular distillation may be conveniently used for materials with molecular weights between about 300 and 1100. The lower limit is set by the need for the material to have a low vapour pressure at the condenser cooling water temperature (20°C.); the upper limit is set by the need for the material to have a high enough vapour pressure at temperatures of 300°C. to 350°C., the highest temperatures to which organic distillands may be subjected without decomposition. Materials of a higher molecular weight may be processed if they possess a greater thermal stability, for example silicones and fluocarbons.

The increasing interest in this method of separation is shown by a number of excellent reviews which have appeared recently. Ridgway Watt[20,21] reviews the various applications of molecular distillation and describes constructional features of different types of still. An excellent monograph by Burrows[22] covers the basic theory of the process, degassing and vacuum technique and the mechanical and physical design of stills.

### Practical aspects of molecular distillation

An efficient still must solve certain problems inherent in this technique. If distillation takes place from a stagnant layer of liquid, the efficiency of the still is soon reduced by depletion of the most volatile component in the surface layer of the liquid. Thus the liquid must be agitated in some way. Consideration must also be given to the fact that most material processed is heat-sensitive and a low liquid residence time in the heated section is required. Finally, at these low pressures, chosen to minimise collision of vapour molecules, vapour flow occurs only between the evaporator and the condenser. If more than one separating stage is required countercurrent flow may be obtained by liquid movement only.

The simplest form of molecular still is the pot still. In this type the liquid is stagnant and the thermal hazard is high, thus it is of little use commercially. However, the pot still is a useful laboratory tool, especially for semi-micro analysis, where the small size of the samples reduces the time required for distillation. A semi-micro pot still has been described by Ungnade.[23]

The commercially widely used centrifugal still employs a rapidly rotating conical shaped evaporator. It is a continuous unit and the feed is pumped to the centre of the inside of the evaporator, where it is accelerated by centrifugal force to flow in a fast thin film over the evaporator surface. Contact times as low as 0·001 sec. have been reported, although the normal range is 0·05-2 sec.[24] Thus this type of still has a very low thermal hazard. The well-known centrifugal still of Hickman has the rotating evaporator driven from underneath the still. A recent modification by Watt[25] drives the evaporator from the top of the still. This facilitates removal of the evaporator for cleaning.

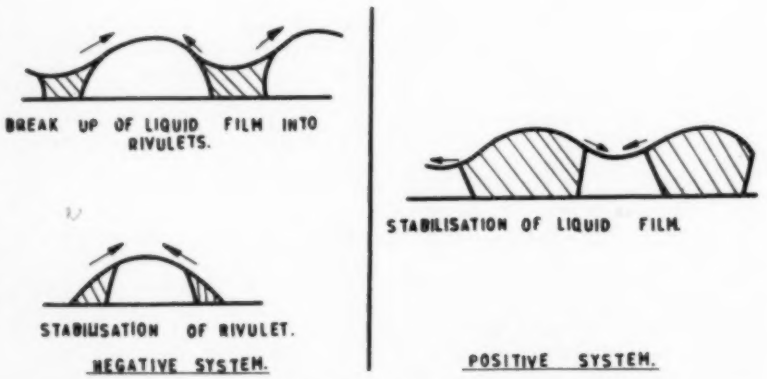


**Fig. 2. Diagrams of liquid films in packed distillation columns. The thin parts of the film are assumed to be more completely saturated with the Least Volatile Component. The arrows indicate the direction of the surface tension forces. Shaded areas denote liquid of lower surface tension. (See F. J. Zuiderweg, ref. 10.)**

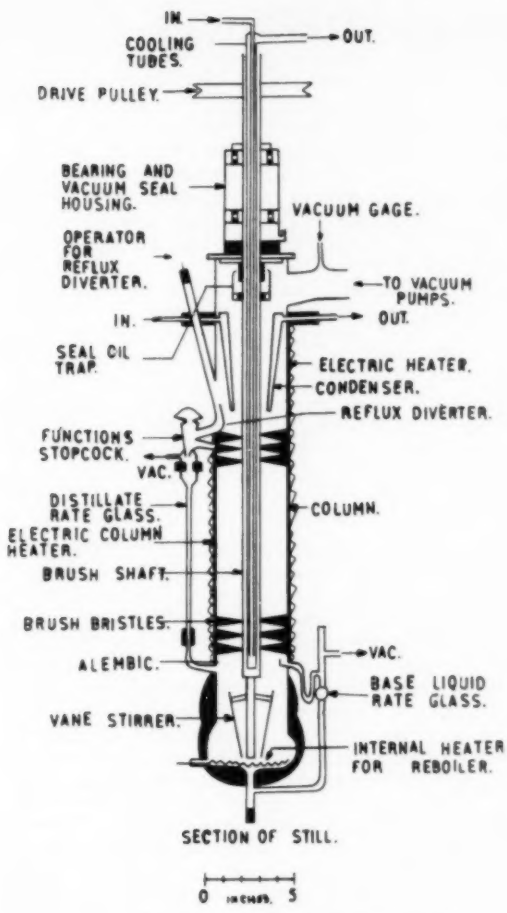


**Fig. 3. The Brush Still (see E. S. Perry, ref. 30).**

Perhaps the most promising new device for commercial molecular distillation is the large-scale wiped film still.[26] The evaporator is a static vertical cylinder with a thin film of turbulent distilland maintained on its inner surface by means of moving wiper blades. These blades also accelerate the liquid, giving a short contact time to reduce thermal hazard. These stills are capable of large throughputs, and being comparatively cheap are serious contenders to the large centrifugal stills for all but the most thermolabile materials.

When more than one stage is needed in a commercial scale molecular distillation this is usually done by interconnecting several single stages. This is discussed by Burrows.[22] On the laboratory scale several multistage fractionating stills have been constructed.[27, 28, 29] Usually the principle of operation is to cause the distilland to flow gently down a sloping evaporation surface. The distillate condenses on cooled plates placed above the evaporator so inclined that the condensate drips back on to the upstream evaporating surface. Thus a countercurrent flow system is obtained which results in the more volatile components accumulating at the top of the apparatus, and the less volatile at the bottom. A continuous fractionating still of this type was described by Malyusov.[29] The column consisted of a sloping tube 890 mm. long by 45 mm. in dia. containing 37 stages.

The main disadvantage of these types of stills appears to be the relatively slow liquid flow which results in appreciable residence times. Thus they are more suited for the treatment of thermally stable materials.

At pressures just above the molecular distillation range fractionation may be achieved by means of the brush still of Perry and Cox.[30] This still, shown in Fig. 3, is 3·5 in. in diameter and 11 in. high. The spiral brush is mounted on a hollow cooled shaft. At speeds up to 1,800 r.p.m. the bristles sweep the wall and produce a uniform layer of liquid on the heated surface. Fractionation occurs by vapour condensing on the cold core and being flung off on to the evaporator. At the maximum liquid rate of 700-800 c.c. per hr. the still has an efficiency of 7-8 theoretical plates and a column pressure drop of less than 1 mm. Hg. Perry[31] has published the results of the distillation of various essential oils. Good results were obtained even with an extremely thermally labile citral oil.

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# Fermentation Technology Advances

*The production of chemicals by micro-organisms is a much more exact technology than it was 20 years ago. The inspiration and incentive has been in the main the manufacture of valuable antibiotics, notably penicillin. Recently in London the Institute of Chemical Engineers ran a symposium on biochemical engineering in which advances in fermentation technology were assessed. Here is a report of the symposium by a pharmacist-chemical engineer followed by condensed versions of two papers, one reviewing developments in techniques and the other equipment for laboratory and pilot-plant fermentations.*

## PHARMACY AND BIOCHEMICAL ENGINEERING

**By H. W. Fowler**

AS IS appropriate for the first symposium on biochemical engineering, the proceedings began with a review of the present position by D. J. D. Hockenhull indicating the scope of fermentation processes, outlining some of the problems and concluding with suggestions of future trends. This review contained the significant statement that there is need " for the biochemist and the engineer to come together, especially over matters such as these discussed here, for thinking about them involves generalised concepts rather than specialised knowledge."

The chemist and the chemical engineer can appreciate readily each other's point of view because part of their training is common to the two subjects and because both are used to dealing with well-defined, physical systems.

The biologist and the engineer, on the other hand, have little or nothing in common. It is essential, therefore, for the two to come together, to enable the engineer to learn something of the difficulties of biochemical processes and to realise that many of his techniques applicable to inanimate chemical systems are useless when living organisms are involved. The biologist, however, generally fails to understand that the engineer must seek design conditions on a generalised and not a specific basis. This point is illustrated by the fact that in the discussion a microbiologist complained that four of the six papers did not name a single micro-organism.

The second paper by R. Elsworth, E. J. Morris and D. M. East was concerned with the heat sterilisation of spore infected air, with the intention of studying the kinetics of air sterilisation and the investigation of time/temperature relationships for design purposes. The results support the suggestion that the sterilisation of air corresponds to a first order reaction and values are given for the constants. Relationships were shown between " penetration " and temperature and also between exposure time and temperature. " Penetration " was used to indicate the surviving organisms and is not an ideal term. It has been inherited from work on air filtration, where its use is apposite. While the data are useful for design purposes, the method is applicable to small-scale operation only.

Prof P. H. Calderbank's paper with S. J. R. Jones was the third in a series on physical rate processes in industrial fermentation. Previous parts have considered oxygen transfer from the gas to the liquid phase. The latest work was concerned with mass transfer from the liquid phase to solid particles. It was an excellent illustration of the chemical engineer's approach to a complex situation. A suspension of particles of ion-exchange resin was used as an analogue of micro-organisms dispersed in nutrient medium. Mass transfer was observed by introducing sodium hydroxide and following the change of *p*H, the results showing that this stage of mass transfer is likely to be rate determining in many industrial fermentations.

Sewage treatment seems to have little in common with antibiotic processes and one's first reaction may be to pass over the paper by A. L. Downing and R. W. Bayley. But the processes have certain similarities, and the work on aeration will be useful in fields other than the treatment of waste waters. The investigations were on rates of oxygen absorption from air bubbles and a range of variables was considered, including bubble size, depth of immersion, various methods of air dispersion and the influence of surface active agents.

It is always useful to have an account of years of experience in the mechanical construction of equipment. E. P. McCann, A. Parker, D. Pickles and D. G. Wright described the construction of and operating techniques for small-scale fermenters, including 5 and 30 litre laboratory versions and 220 gall. pilot plant units. Results were given for oxygen transfer rates. It might have been useful to have quoted further illustrative data for experimental fermentations.

The papers ended with a report of further work on aeration, this being a field in which the chemical engineer can make a considerable contribution. N. Blakeborough, G. Hamer and M. W. Walker have investigated mixing and aeration in vessels and have shown that surface aeration is unimportant in the circumstances considered and that areas of no aeration and little agitation may occur unless the equipment is properly designed.

The symposium closed with a discussion of the papers. Many comments emphasised the difference in thought between the biologist and the engineer. If biochemical

engineering is to succeed, these points of view must be united and a person is required having training and background in both fields. Having qualified in both pharmacy and chemical engineering, my experience suggests that the pharmacy graduate is best suited for this work. Pharmaceutical training includes the necessary biological aspects as well as a background of physical and chemical principles and the rigorous treatment of data. If such a person amplifies his knowledge of the technological side, as is given by the honours subject of Pharmaceutical Engineering Science in the University of London degree in Pharmacy, a bridge is provided between the specialist biologist and the specialist engineer.

# LESSONS FROM PENICILLIN PRODUCTION

By Dr. D. J. D. Hockenhull*

THE production of commercially valuable compounds by micro-organisms is essentially based upon diversion of the normal biochemical pathways responsible for growth and reproduction. This diversion may be brought about by:

(1) overfeeding with special nutrients,
(2) deprivation of air,
(3) lack or inhibition of biological catalysts,
(4) the addition of trapping agents,
(5) exploitation of inborn errors in metabolism.

Examples include the microbiological production of vinegar, ethanol, citric acid, lysine and the antibiotics. In all these examples the aim is to impose a nutritional pattern on a particular micro-organism so that the desired end-product accumulates in a high yield.

This concept is well illustrated by the history of penicillin manufacture. The ultimate building stones of penicillin are valine, cysteine and a substituted acetic acid (penicillin G).

The substituted acetic acid is derived from cornsteep liquor (more recently various ethanol-amides that release the acid more slowly have been favoured). Valine is derived from sugar and cysteine arises in the latter stages of metabolism. Thus there exists on the normal metabolic equipment of the organism the chain of reactions indicated in Fig. 1 that could lead to the components of penicillin. The problem is to arrange the conditions to favour the production of the two amino acids. Much work has already been done in making the organism more prone to form these precursors by mutation and to select strains of higher productivity.

Initially commercial production of penicillin was produced by surface culture of the organism. More complex ingredients were added and finally a medium containing cornsteep liquor fortified with extra phenylacetic acid derivatives was adopted and is still used today.

It was then found that penicillin could be produced in deep culture. This led to the development of the present conventional vessel, a baffled vertical tank with air sparged in at the bottom and a number of paddles on a vertical shaft for mixing and air dispersion. This vessel raised new problems: the supply of large metered volumes of sterile air; the development of bacterium-tight fermenters; development of systems for air exchange and mixing in the fermenters; control of foaming; supply of steam for sterilisation; and problems

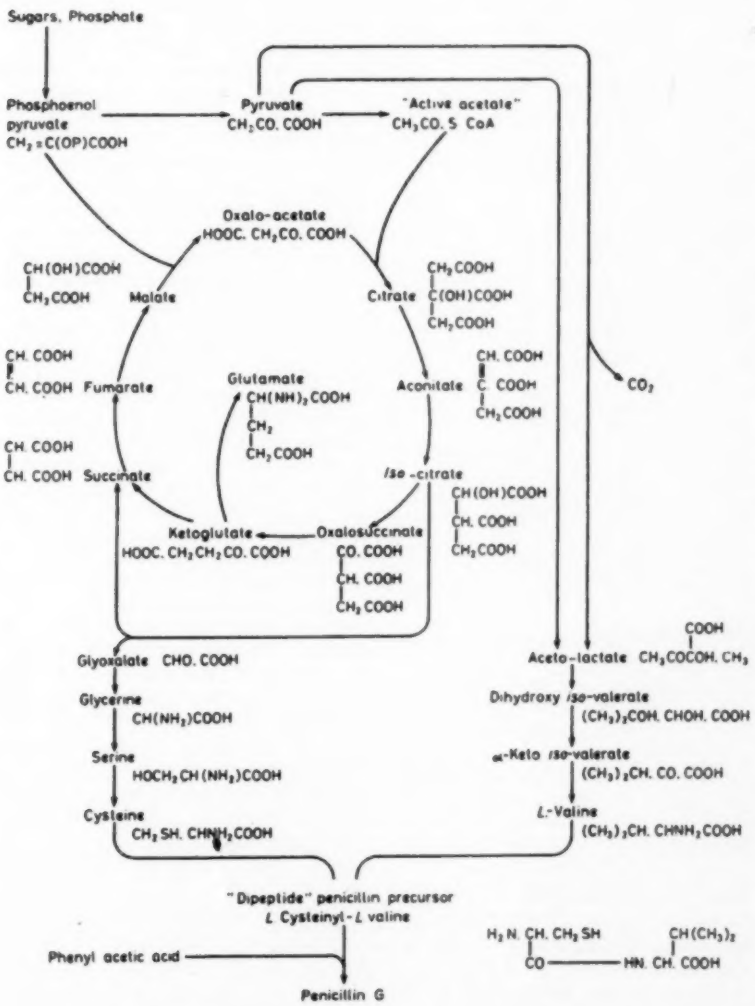


**Fig. 1. A metabolic map for the manufacture of penicillin G.**

* Glaxo Laboratories Ltd.

of cooling arising from the metabolic heat generated. Many papers have been published dealing with fermenter design.

From this batch stage the logical step was to continuous supply of nutrients and then to completely continuous fermentation. Important development work by Marvin Johnson and his group covered equipment for producing the antibiotic by continuous addition of glucose and phenylacetic acid, while controlling *p*H by adding acid or alkali. These operations produced many new mechanical problems. Pumps and metering equipment must withstand sterilising temperatures and must deliver sterile solutions according to a set programme. Methods also had to be devised for measuring *p*H and other values of biological importance. Moreover, the problems of biological fouling and " drift " are not completely solved.

In other fields complete processes have been evolved for continuous fermentation; one interesting practical application is a plant to manufacture baker's yeast operated by the Distillers Co.

### Future trends

The emphasis of future development must therefore be on the examination of rates of nutrient supply (including air) as a pattern for the whole fermentation and establishment of the optimal ratios of these rates to each other. In other words, we must abandon the old procedure of just arranging the initial conditions, loading up the fermenter, setting off the fermentation, and letting it drift on whatever metabolic winds and tides that may spontaneously occur. We have to steer the course of the fermentation throughout, taking into account such biochemical landmarks as *p*H value, sugar level, and mycelial weight. It is for the automation of such processes that the engineer will be called on to make his most important contribution in the future, although at present the biologist has still to determine what criteria are to be chosen for this regulation and how they are to be programmed. There is, however, a similar need for the engineer to design control equipment for use by non-engineers, and thus also for the biochemist and the engineer to come together, especially over matters such as those discussed here, for thinking about them involves generalised concepts rather than specialised knowledge.

# LABORATORY AND PILOT-PLANT FERMENTERS

By E. P. McCann, A. Parker, D. Pickles and D. G. Wright*

THE RAPID developments in the past two decades in antibiotics manufacture and research have created a demand for laboratory and pilot plant which could be used for studying aerobic submerged cultures to translate these processes to the full manufacturing scale. Rotary shaking machines used for many individual cultures have enabled problems to be tackled on a broad base, as well as selecting promising strains and combinations of variables that give the highest yield. However, characteristics of shaken cultures differ in practice from those of stirred, aerated cultures on a large scale, and it is general practice to employ small-scale fermenters to confirm or modify the preliminary findings from shaken culture.

### Laboratory fermenters

Laboratory fermenters are classified as having a capacity of 30 l. or less and are sufficiently portable to be sterilised in an autoclave and to be cooled in a temperature controlled bath. There are several shortcomings; the medium cannot be stirred during autoclaving; several fermenters in one constant temperature bath may result in larger variations in temperature of the culture than in bigger installations with individual control; and aseptic techniques are generally based on normal microbiological laboratory practice.

### Pilot plant

Fermenters on this scale are arbitrarily defined as those over 30 l. capacity, fixed, jacketed or coiled for heating and cooling and the requisite services permanently connected. There are various descriptions of pilot plant in the literature for various scales of working.

### Five-litre fermenters

Some features of the design and operation of laboratory fermenters can be illustrated by the following references to the authors' designs for 5 l. and 30 l. fermenters.

*Layout of fermenter bench.* A 1½ h.p. motor drives the main shafting at 550 r.p.m. and by appropriate pulleys individual drives are transmitted to the 24 fermenters. Fittings and belts are adjustable so that agitation rates of 440, 550, 800 and 1,050 r.p.m. are possible. A simple coupling allows some latitude in the positioning of the fermenters under the drives.

*Temperature control system.* The fermenters are immersed in baths about 6 in. deep through which water at a controlled temperature is circulated, giving a control of approximately ±0·5°C. The fermenter temperature is about 1°C. above that of the water and the degree of control is found to be adequate.

*Instrument panel.* This includes air rotameters measuring air to the individual fermenters, a two-pen recording thermometer, and an air pressure recorder which gives a time and pressure record of the operation of the antifoam dosing-controller also situated on the panel.

*Antifoam dosing controller.* Small quantities of antifoam are added at regular intervals. An adaptation of a pneumatic temperature controller operated by a cam system supplies air to a manifold running along the front of the baths, putting the system under pressure and blowing antifoam from the dosers connected to it, into the fermenters.

*Description of the fermenter.* The fermenter consists of a stainless steel cylinder which can be bolted to the bath. The agitator gland-housing is in the centre of the lid. The lid also carries the charge hole, the sampling and inoculation tube, the air inlet and air outlet, and the antifoam and spare addition ports. The sampling dip-leg had a baffle attached which breaks the vortex caused by the four-bladed stirrer.

*Air filters, sampling and antifoam dosers.* The air fed to the fermenters is filtered through tightly packed cotton-wool. Sampling is done *via* neoprene rubber tubing attached to the dip-leg. At the end of the tube is a special aluminium cap to which

* I.C.I. Pharmaceuticals Division.

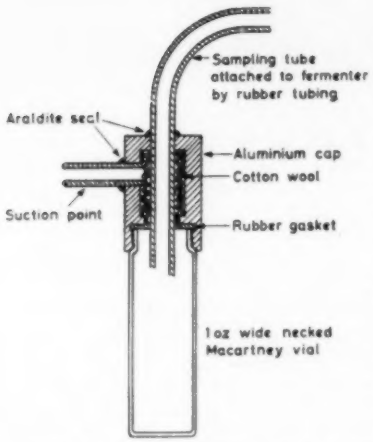


**Fig. 2. Sampling point for a 5 l. fermenter.**

is attached the sampling bottle (Fig. 2). Care is taken to ensure that the bottle is carefully sealed and suction air is filtered to ensure sterility.

The antifoam doser consists of a hypodermic needle leading from the doser to the antifoam addition branch of the fermenter. When the manifold is put under air pressure by the operation of the controller, the antifoam oil is blown through the needle into the fermenter.

*Operation of the fermenters.* Before operation, all parts of the fermenter are checked for cleanliness, while air outlets are plugged with cotton-wool and capped and other outlets are sealed. The medium is prepared and then charged to each fermenter. After sealing, the fermenters are sterilised and fitted to the bath. Air flow is started and the agitators are set running just before inoculation.

Inoculation with spores or similar small quantities of inoculum is done through the charge hole. Larger amounts of vegetative inoculum are added by a semi-enclosed method and blown over *via* the sampling point on the fermenter.

## Thirty-litre fermenters

*Layout.* These fermenters are accommodated in three-seater baths which are arranged back to back, with driving equipment, water circulation system and control panels between them. Sited on the control panels are the air rotameters, electronic relays for the "on demand" antifoam system, and electric motors and gear boxes. These driving shafts protrude from the panels and are connected to the fermenters by flexible couplings. The agitation speeds available from combinations of the pulleys are 250, 350, 450 and 510 r.p.m. approximately.

*Description of fermenter.* The general structure is similar to that of the 5 l. fermenter except that the lid also carries a thermometer pocket and a socket for the antifoam electrode. The sparge ring lies directly under the six vertical agitator blades and the actual agitator shaft is slotted to engage with the flexible coupling.

*Sampling point.* This is similar to those used on the 5 l. fermenters except that instead of being packed with cotton-wool it has a separate cotton-wool filter attached to the suction point.

*Antifoam dosers.* These are carried on the side of the fermenter lid in a heating jacket to maintain them at about 80°C. The inlet end of the doser is connected to the appropriate air supply point and the dip leg arm terminates in a No. 11 serum needle which is inserted through the rubber diaphragm of the addition point.

*Antifoam addition method.* This is similar to the 5 l. scale except that larger needles are used and the doser is enclosed in a heating jacket to allow a wider choice of material to be used. The "on-demand" system used employs a suspended electrode which when contacted by rising foam causes a change in the resistance of the circuit which operates a relay opening a valve admitting compressed air to the doser.

*Provision of continuous nutrient feed.* To feed sugar or other nutrient solution to the fermenter a small electrolytic cell is employed that produces gas at a uniform rate and displaces the feed through a tube connected to the chargehole of the fermenter.

## Pilot plant fermenters

The pilot plant fermenters are cylindrical stainless steel jacketed vessels of 220 gal. capacity. The agitator is a disc carrying six blades welded to its periphery. A sparger situated below the disc directs the air stream towards the lower face of the disc. Four baffles are mounted radially and symmetrically to the wall of the fermenter. A 20 h.p. motor running at 1,440 r.p.m. is connected to a gear box. Suitable pulleys allow a range of agitator speeds between approximately 150 and 300 r.p.m. to be selected.

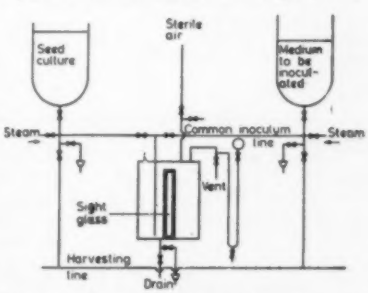


**Fig. 3. Transfer of seed cultures in a pilot plant.**

A bottom run-off branch is provided for liquid transfer to and from the vessel. The remaining branches connecting the various services mostly enter *via* the cylindrical part of the vessel above the liquid level (160 gal. volume). The lid is kept as free as possible for easy servicing and carries illuminated sight glasses, foam detecting electrode, thermometer pocket, air vent line and charge hole for raw materials.

Instruments include a temperature recorder/controller and an air flow indicator. The insulated foam detecting electrode is coupled to a relay which operates an alarm bell and a warning light.

*Air sterilising filters.* Each fermenter has its own air sterilising filter made of two slag wool pads.

*Agitator shaft gland.* This provides one of the main hazards to the maintenance of pure culture conditions. Conventional stuffing boxes are difficult to sterilise and to maintain sterile during culture. Trials have shown that a gland packed with *Plastalloy* topped with a ring of *Supeta* packing would remain leakproof and maintain pure culture conditions for up to 8 days' duration. Between fermentations the gland is checked by pressure testing.

*Preparation of seed culture.* The usual practice in the authors' organisation is to use one fermenter to prepare sufficient seed culture to inoculate several fermenters, thereby comparing several sets of variables using one common culture. Seed cultures are generally prepared in the laboratory by surface or submerged culture. If the mould does not produce conidia readily then a suspension of vegetative cells is produced to provide the inoculum for the seed culture. The final laboratory starter culture is then introduced by aseptic methods into the fermenter.

*Transfer of seed culture to cultures for product formation.* This is normally done when the seed culture is approaching its maximum cell con-

(*Continued on page* 378)

# Rauwolfia—*ANCIENT DRUG, MODERN TRANQUILLISER*

By William E. Court,* M.Pharm., F.P.S., F.L.S.

*In spite of the appearance of synthetic competitors, the Rauwolfia drugs remain among the major psycho-pharmaceuticals. Although used medicinally in India for hundreds of years, the modern history of Rauwolfia began only 15 years ago. During that time a great deal of effort has gone into the analysis and standardisation of Rauwolfia derivatives. The extent and thoroughness of this work can be judged from this specially contributed review.*

THE investigation of the indigenous plant *Rauwolfia serpentina* Benth. by the Indian chemists Siddiqui and Siddiqui in 1931[1] initiated a vast amount of research into the genus Rauwolfia in all parts of the world. Such widespread research endeavour embraced a variety of disciplines. Botanists sought to establish the identity of the many different Rauwolfia species; pharmacognosists described the structural characteristics and compared the microscopical features of differing species and, together with chemists, tried to isolate alkaloids and assay them; pharmacologists attempted to explain the actions of the crude drug extracts and isolated alkaloids on test animals; medical practitioners endeavoured to apply these findings in clinical practice, and more chemists commenced the study of the synthesis of Rauwolfia alkaloids and their analogues.

Prior to 1952 no correlation between chemical assay and biological assay or effect had been observed, but in that year Mueller, Schlittler and Bein published details of the isolation of a feebly basic indole alkaloid, reserpine, which exhibited the typical pharmacological characteristics of *Rauwolfia serpentina* extracts.[2] This discovery stimulated further widespread research, which is still proceeding.

## Botanical survey

The genus Rauwolfia comprises a group of tropical woody shrubs and trees belonging to the family Apocynaceæ, and classified in the alkaloid yielding subfamily Plumeroideæ.[3] One hundred and seventy-two species have been listed in the Kew Index and its supplements, but closer investigation has revealed considerable synonymy and the work of Pichon,[4] Woodson,[5] Rao[6] and Bisset[7] has reduced the genus to about 76 species. Of these 34 species occur in Central and South America, 17 species in Africa, 7 species in India and Burma and the remainder in the Far East and the Pacific Islands (Fig. 1).

The Rauwolfia species vary greatly in size and habit, the smallest being the African sub-shrub *Rauwolfia nana* E. A. Bruce which is barely 6 in. high, and the largest the Peruvian tree *Rauwolfia præcox* K. Schum. which often exceeds 100 ft. Three species in particular are widely distributed—*Rauwolfia serpentina* in India and Burma, *Rauwolfia vomitoria* Afz. in Africa extending from Gambia in the west to Kenya in the east and Mozambique in the south, and *Rauwolfia tetraphylla* L. (=*R. conescens* L. = *R. heterophylla* Roem. and Schult.), a species indigenous to Central America and introduced into India and Australia. All three have been extensively studied and are important articles of commerce.

## Chemical constituents

The principal constituents are indole alkaloids (Table 1) and can be grouped under four headings:

1. The yellow, strong anhydronium bases, *e.g.* serpentine, serpentinine, alstonine.
2. The colourless, tertiary indoline alkaloids which are of intermediate basicity, *e.g.* ajmaline, iso-ajmaline, rauwolfinine, tetraphyllicine.

**Table 1. Principal Alkaloids in Commercial Rauwolfia**

| *Alkaloid* | *Empirical formula* | *R. serpentina* | *R. tetraphylla* | *R. vomitoria* |
|---|---|---|---|---|
| Anhydronium bases | | | | |
| Alstonine | $C_{21}H_{20}O_2N_2$ | − | + | + |
| Serpentine | $C_{21}H_{20}O_3N_2$ | + | + | − |
| Serpentinine | $C_{21}H_{20}O_3N_2$ | + | − | + |
| Tertiary indoline bases | | | | |
| Ajmaline | $C_{20}H_{26}O_2N_2$ | + | + | + |
| Isoajmaline | $C_{20}H_{26}O_2N_2$ | + | + | − |
| Tetraphyllicine | $C_{20}H_{24}O\ N_2$ | − | − | + |
| Tertiary indole feeble bases with heterocyclic ring E | | | | |
| S-yohimbine (ajmalicine) | $C_{21}H_{24}O_3N_2$ | + | − | + |
| Aricine | $C_{22}H_{26}O_4N_2$ | − | + | − |
| Reserpiline | $C_{23}H_{26}O_5N_2$ | + | + | + |
| Reserpinine | $C_{22}H_{26}O_4N_2$ | + | + | − |
| Isoreserpiline | $C_{22}H_{26}O_5N_2$ | − | + | + |
| Tertiary indole feeble bases with carbocyclic ring E | | | | |
| Reserpine | $C_{33}H_{40}O_9N_2$ | + | + | + |
| Rescinnamine | $C_{35}H_{42}O_9N_2$ | + | − | + |
| Deserpidine | $C_{32}H_{36}O_6N_2$ | + | + | − |
| Yohimbine | $C_{21}H_{26}O_3N_2$ | + | + | + |
| Corynanthine | $C_{21}H_{26}O_3N_2$ | + | + | − |
| Sarpagine | $C_{19}H_{22}O_2N_2$ | + | + | − |

\+ alkaloid reported as present.
− alkaloid not reported.

Further information: Schlittler, "Rauwolfia" (Little, Brown and Co., Boston), 1957. Bisset, *Ann. Bogor.*, 1958, **3**, 179–235.

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3. The colourless, feebly basic tertiary indole alkaloids with a heterocyclic ring E (tetrahydroalstonine type), *e.g.* reserpiline, aricine, tetrahydroserpentine, reserpinine, δ-yohimbine (=ajmalicine).
4. The colourless, feebly basic tertiary indole alkaloids with a carbocyclic ring E (yohimbine type), *e.g.* reserpine, rescinnamine, deserpidine, stereoisomers of yohimbine, corynanthine, serpine, isorauhimbine, rauwolscine.

The distribution of the alkaloids varies in quantity and relative ratio in different species and in the same species obtained from different geographical sources. The alkaloids are found mainly in the root bark of the plants, the wood yielding very little alkaloid.[8]

Pharmacologically, the most interesting alkaloids are the yohimbine type feeble bases, reserpine, rescinnamine and deserpidine, the first named being the most important. Assay of these bases must be preceded by an isolation technique which yields the required alkaloid reasonably free from contamination.

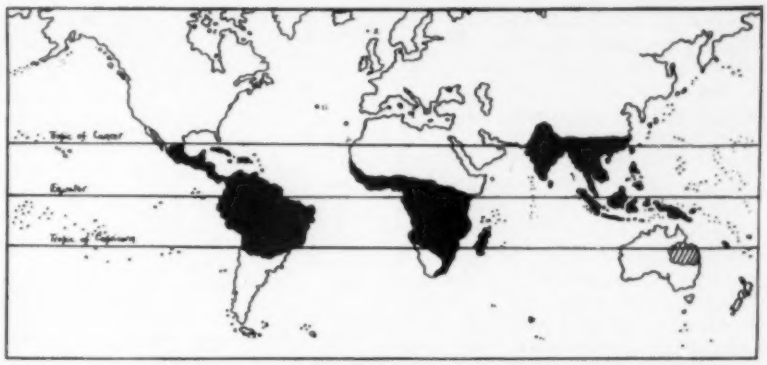


**Fig. 1. World distribution of *Rauwolfia* species. Black areas indicate zones in which *Rauwolfia* species grow. Shaded area of Australia indicates where *Rauwolfia tetraphylla* has been introduced.**

## Separation of the weak bases

The simplest method for separating the feeble bases is extraction in chloroform from an acid solution of the total alkaloids. The mixed feeble bases, however, require further separation.

Banes, Carol and Wolff[9] demonstrated the efficiency of a paper chromatographic system employing an iso-octane—benzene—cyclohexanol mobile phase and a formamide-acetone stationary phase.

An alternative mobile phase, *n*-heptane-carbon tetrachloride — *t*-butyl alcohol was also recommended.[10] A similar system was employed by Korzun, St. Andre and Ulshafer, the stationary phase being formamide-methanol and the mobile phase benzene-cyclohexane.[11] All three systems separate the important alkaloids reserpine, rescinnamine and deserpidine from each other and from the more basic alkaloids. Other successful systems reported include methyl alcohol — acetic acid — sodium acetate and isobutylmethylketone (Khan)[12] and heptane—ethylmethylketone and formamide (Kaiser and Popelak).[13]

Some workers have used cellulose chromatographic columns[14] although the limitations of such columns have been stressed.[15] Cellulose columns do not separate the feeble bases efficiently, but Hayden, Ford and Houk successfully employed a *Celite* 545 (diatomaceous silica) column impregnated with formamide. On elution with *n*-heptane—morpholine—chloroform saturated with formamide, the feeble bases were delivered separately in the sequence deserpidine, rescinnamine and reserpine.[16]

Paper electrophoresis is another modern technique successfully applied to this separation problem. Sakal and Merrill[17] and Sahli[18] employed 5 N acetic acid as electrolyte, but Paris and Dillemann[19] used 2 N formic acid.

The distribution of Rauwolfia alkaloids between immiscible solvents in the countercurrent distribution apparatus was investigated by Kidd and Scott, who recommended the use of ether-chloroform (3 : 1) and *p*H 3·1 buffer solution for the separation of reserpine from total alkaloid extracts.[20] By using chloroform and selected phosphate buffers Bannerjee, Chatterjee and Hausler were able to obtain eight distinct fractions from a total alkaloid extract of *Rauwolfia serpentina*.[21]

In all these separation procedures the positions of the principal Rauwolfia alkaloids on the papers, or columns, or in tubes, can be detected by their fluorescence in screened ultra-violet light.

## Chemical assay

A wide range of modern assay techniques has been used to estimate Rauwolfia in terms of its content of reserpine, the most important active principle.

Early workers exploited the ultraviolet absorption characteristics of pure reserpine and methods of assay based on absorbances at 259·25 mμ, 275 mμ, 267 mμ and 295 mμ were evolved.[14,17,22,23] Reserpine can be identified by the ratio of the absorbances at 267 mμ and 295 mμ (1·83) or at 267 mμ and 275 mμ (1·14).[14] For pure reserpine, absorbances at 275 mμ and 259·25 mμ are equal.[14] Calculation of the reserpine content is based on the 267 mμ absorbance, reference being made to a standard curve.

Reserpine readily undergoes alkaline hydrolysis yielding reserpic acid, 3-4-5-trimethoxybenzoic acid and methanol (Fig. 2). The first two hydrolytic products interfere with the absorbancy measurements on the genuine alkaloid, and this can be eliminated by washing the chloroform solution of reserpine with 0·01 M hydrochloric acid to remove the reserpic acid and with 1% solution of sodium bicarbonate to remove the 3-4-5-trimethoxybenzoic acid.[23]

In another spectrophotometric

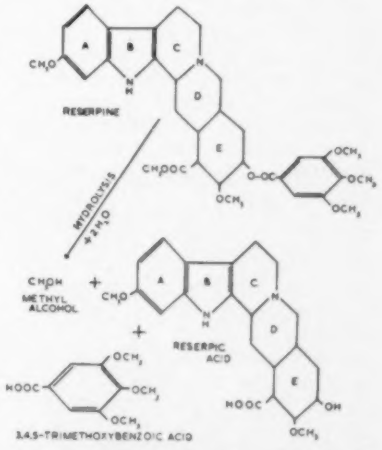



**Fig. 2. Hydrolysis of reserpine in alkaline solution.**

method which is capable of detecting microquantities of reserpine (0·25 $\mu$g. per ml.), the powdered root (1 g.) is extracted with chloroform in a micro Soxhlet apparatus for 4 hr. After filtration the volume is adjusted with chloroform and an aliquot taken. This portion is washed four times with 0·1 N hydrochloric acid, 0·05 N sulphuric acid is then added and the chloroform removed by heating on a waterbath. Washing the acid solution with benzene removes rescinnamine and other interfering substances and the reserpine is recovered by extraction in chloroform. The estimation is completed by measuring the absorbance at 268 m$\mu$.[24]

McMullen and his co-workers observed that reserpine could be readily converted to fluorescent products by heating with strong acids.[23] Dechene noticed that reserpine in acid solutions was slowly oxidised to yield fluorescent substances, and devised a technique of accelerated oxidation of reserpine in 5 N acetic acid using hydrogen peroxide. The fluorescent product was proportional to the reserpine present even at concentrations as low as 0·02 $\mu$g. per ml.[25] Subsequently he showed that the oxidation products of reserpine, and particularly 3-dehydroreserpine, do not interfere with the estimation.[26]

Various colorimetric procedures have been proposed. Booth exploited the formation of a chloroform soluble dye complex with bromophenol blue.[27] Banes employed the red colour formed when an indole nucleus reacts with vanillin reagent,[28] and De Felice used the organic solvent soluble complex formed with methyl orange.[29] Szalkowski and Mader developed a rapid method depending on the greenish-yellow colour produced when ethanolic solution of reserpine reacts with sodium nitrite and sulphuric acid.[30] This method was modified to eliminate interfering substances.[31] Haycock and Mader[32] investigated the complex and showed that it was specific, no coloured complex being formed with alstonine, rauwolscine, sarpagine, yohimbine or deserpidine. They established that the 7-methoxy-$\beta$-carboline group, *i.e.* the 11-methoxy group and the A, B and C ring skeleton of reserpine (Fig. 3), is the functional group necessary for production of the coloured complex under the conditions of the assay. Thus rescinnamine produced chromogenic values approximately

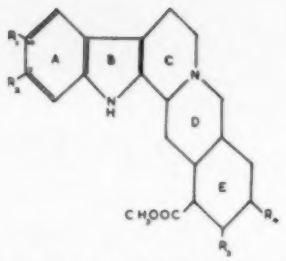
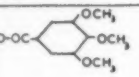
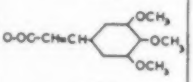
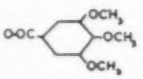
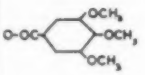



**Fig. 3. Feebly basic tertiary indole alkaloids with a carbocyclic ring E. (Key below.)**

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| RESERPINE | H | $CH_3O$ | $CH_3O$ |  |
| RESCINNAMINE | H | $CH_3O$ | $CH_3O$ |  |
| DESERPIDINE | H | H | $CH_3O$ |  |
| RAUWOLSCINE<br>YOHIMBINE<br>CORYNANTHINE | H | H | OH | H (STEREOISOMERS) |
| RAUNESCINE | H | H | OH |  |

equal to reserpine. Reserpinine, a tertiary indole with a heterocyclic ring E and an 11-methoxy group formed the greenish-yellow complex, as did reserpiline, the 10 : 11-dimethoxy variant (Fig. 4). Aricine (Fig. 4), which possesses the 10-methoxy group, produced only a weak reaction after several hours, and raunescine, which has no 11-methoxy group, produced no colour complex. A blank estimation is essential and estimates the substances absorbing light at 390 m$\mu$ prior to the nitrite treatment.[31] A similar, but more recent, method has been proposed. The sodium nitrite is added to an acetic acid solution of the alkaloid and the mixture heated on a boiling waterbath for 5 min. The coloured complex formed is extracted in chloroform and measured at 465 m$\mu$, the orange colour of the degradation products not being extracted.[33]

Two titration methods were published by Bayer in 1956.[34] In the first an anhydride-free glacial acetic acid solution of reserpine was titrated with 0·1 N acetic acid solution of perchloric acid using crystal violet in acetic acid as indicator. The error of the determination was less than $\pm$0·3%. The other method, a microdetermination, was dependant on the reaction of a chloroform solution of reserpine with 0·005 N chloroform solution of *p*-toluene sulphonic acid, the indicator being *p*-aminoazobenzene in chloroform and the error less than $\pm$0·6%. A similar, non-aqueous titration method appeared in 1958, the chloroform solution of reserpine being titrated with 0·002 N solution of *p*-toluenesulphonic acid in ethylene glycol-isopropyl alcohol (1 : 1).[35]

## Choice of method

Under ideal conditions all these methods yield accurate and reproducible results. Choice of procedure is therefore dependent on the quantity of material available, the relative proportions of closely related alkaloids, the nature and amount of the vehicle or excipient and the presence of degradation products.

Rescinnamine in particular interferes with reserpine estimations, but, as it is pharmacologically similar to reserpine, some workers have sug-

gested the use of the reserpine-rescinnamine content as an index of activity.[10] Rescinnamine can be estimated in the presence of reserpine either by exploiting the reactivity of the double bond of the trimethoxybenzoic function with bromine or by measurement of the ultra-violet absorbances at 268 mμ and 308 mμ and calculation of the rescinnamine present using a two point formula. Spectrofluorometry can also be employed, activation at 310 mμ causing fluorescence at 455 mμ for rescinnamine but not reserpine. The fluorescence of oxidation products cannot be used, because the fluorescence spectra of rescinnamine and reserpine are identical under these conditions.[36] In general, the rescinnamine content of total alkaloid extracts is lower than the reserpine content (Table 2).

**Table 2. Occurrence of Feeble Bases in Commercial Rauwolfia Roots**

| *Name* | *R. serpentina* | *R. tetraphylla* India | *R. tetraphylla* Central America | *R. vomitoria* |
|---|---|---|---|---|
| Reserpine .. .. .. | 0·09-0·16% | 0·07-0·09% | 0·03-0·09% | 0·005-0·22% |
| Rescinnamine .. .. .. | 0·04-0·07% | — | — | 0·04% |
| Deserpidine .. .. .. | 0·003-0·006% | 0·04-0·08% | 0·002-0·005% | 0·005% |

Further information: Banes, Houk and Wolff, *J. Amer. Pharm. Ass. Sci. Ed.*, 1958, **47,** 625; and Bisset, *Ann. Bogor*, 1958, **3,** 179–235.

## Formulation and storage

Stability of liquid Rauwolfia preparations depends on the vehicle used and, for reserpine injections, the recommended solvents are weak acid solutions, such as citric, malic and phosphoric acids, stabilised with urethane, carbowax, polyethylene glycol, propylene glycol or benzyl alcohol and adjusted to the optimal *p*H 3.[37]

Rauwolfia preparations must be stored away from light or in amber glassware and the exclusion of oxygen or addition of an antioxidant is advantageous. Recommended antioxidants include butylhydroxyanisole, hydroquinone, nordihydroguaiaretic acid and propyl gallate; sodium metabisulphite is not advised.[38]

## Pharmacology and therapeutic value

The pharmacological activity of the Rauwolfia drugs is due to reserpine, an alkaloid which acts slowly, lowering the blood pressure and producing marked sedation. The sedation is not narcotic and is spectacularly demonstrated with wild animals which become easily manageable. The effect is prolonged and therefore the drug is a tranquilliser. Reserpine seems to act principally in the brain and central nervous system and depletes the tissue stores of 5-hydroxytryptamine in the brain.[40]

Clinically reserpine has been widely employed in the treatment of mild hypertension and psychiatric conditions. Certain side effects such as fatigue, nasal stuffiness, bradycardia, diarrhœa, Parkinsonism and nightmares have been recorded and also acute depression, suicidal tendencies[41] and gastric ulcer[42] in a few cases. For this reason Laurence and Pond[43] opposed the indiscriminate use of these drugs and the Rauwolfia drugs are now included in Section B of the Fourth Schedule to the Poisons Rules 1960, sale to the public being on prescription only.[44] Reserpine depression has been shown to be alleviated slowly by the monoamine oxidase inhibitor, *Iproniazid*.[45] Mild suppression of mental alertness is quite common during Rauwolfia medication and may be a serious handicap to brain workers.[46]

Combinations of Rauwolfia alkaloids in synergistic alliance with pentapyrrolidinium, pentolinium, mecamylamine, hydrallazine, hexamethonium and pentacynium have been proposed for the treatment of hypertension, particularly in patients who are emotionally unstable, but such combinations do not permit the necessary flexibility in treatment and often contain ineffective amounts of the various constituents.[47]

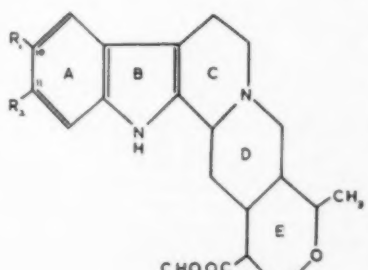



**Fig. 4. Feebly basic tertiary indole alkaloids with a heterocyclic ring E. (Key below.)**

| | $R_1$ | $R_2$ |
|---|---|---|
| ARICINE | $CH_3O$ | H |
| RESERPILINE | $CH_3O$ | $CH_3O$ |
| RESERPININE | H | $CH_3O$ |

The administration of reserpine and triiodothyronine for the treatment of primary Raynaud's disease of the upper limb has given promising results[48] and reserpine has been of some value in the treatment of Huntington's chorea, choreic movements being decreased.[49] In allergic conditions such as asthma reserpine has limited value, although the tranquillising effect relieves the patient's mind of distressing symptoms.[50]

Reserpine is especially valuable in the treatment of psychiatric conditions,[41] being an ataractic, a substance which reduces emotional activity and excitement without narcosis. Maggs and Ellison[51] have described its value in the treatment of schizophrenia with florid psychotic behaviour over a period of five years, and Goldman and Zamansky[52] have emphasised the advantages of tranquillisers in improving the ward behaviour of psychotic patients.

To summarise, the main value of these drugs is in the treatment of severe psychotic excitatory states, whether organic, manic or schizophrenic. Rauwolfia is extremely useful in patients suffering from mild hypertension with emotional disturbance, but is of little value in the treatment of neurotic symptoms. Anxiety is biologically valuable and should only be alleviated if abnormal.[53] Rauwolfia drugs are contraindicated if there is a history of mental depression or gastric ulcers.

## Other Rauwolfia alkaloids

Clinical trials with other Rauwolfia alkaloids or derivatives have not yielded startling results. Rescinnamine is generally regarded as being less effective than reserpine and is unlikely to offer any useful advantage over reserpine in the treatment of hypertension.[54]

Deserpidine (= canescine = raunormine = recanescine = 11-desmethoxyreserpine) produces effects which are not significantly different from those produced by

reserpine, although the sedative and hypotensive effects are apparently weaker.[55] Syrosingopine, carbethoxysyringoyl methyl reserpate, is a derivative of reserpine which demonstrates reserpine-like actions with lower potency and a lower incidence of side effects.[56] Thus there is a wider margin of safety in its clinical usage; 1 mg. syrosingopine is approximately equivalent to 0·25 mg. reserpine or 50 mg. of *Rauwolfia serpentina* root.[57]

**Future prospects**

Although reserpine has been synthesised in the laboratory[58] and numerous synthetic analogues have been produced, there is as yet no substitute for the natural material. During the past decade *Rauwolfia serpentina*, *Rauwolfia tetraphylla* and *Rauwolfia vomitoria* have become important sources of materials which supplement the physician's armamentarium in the field of psychiatry and aid the pharmacologist in understanding of the function of the human brain. Until this knowledge is forthcoming, and probably afterwards as well, Rauwolfia will continue to be required and the galaxy of modern scientific techniques will still be harnessed to the story of an ancient drug that was once almost forgotten.

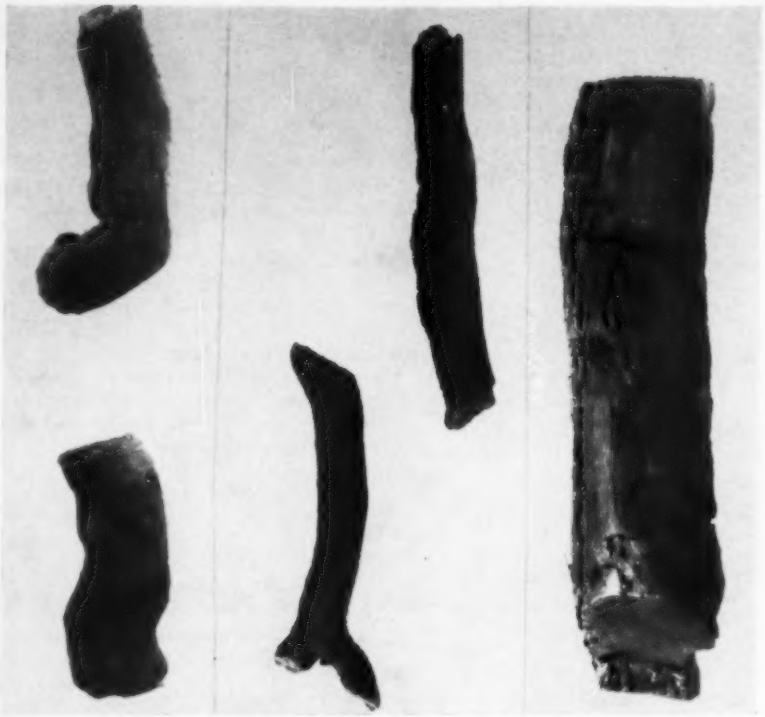


**Fig. 5. Commercial *Rauwolfia* roots. Left: Two roots of *Rauwolfia serpentina*; centre, two of *Rauwolfia tetraphylla* (Indian); and right, *Rauwolfia vomitoria*.**

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# *Odour Counteraction in Industry*

**By R. W. Moncrieff, B.SC., F.R.I.C.**

*The public's nose is getting more sensitive and there is less disposition to tolerate bad smells from factories and sewage farms. This has stimulated the development of several methods of counteracting odours, ranging from combustion and absorption to obliteration with masking compounds. Mr. Moncrieff is an authority on olfaction, and here he explains how bad smells can be suppressed in a variety of industries and situations.*

IT HAS long been known that one sensation can counteract another. Specific tastes that when mixed gave nearly tasteless mixtures were reported by Luchtmans,[1] Oehrwall[2] and Kiesow.[3] More than 100 years ago Valentin[4] noted pairs of odours that mutually counteracted each other. Aronsohn[5] in 1886 specified camphor and petroleum as one pair and cologne water and juniper oil as another. Seventy years ago Piesse[6] wrote:

> "Where there are disagreeable odours, and it is at the same time impossible to get rid of them by an air current, probably the best neutraliser is another odour."

Odour counteraction as a natural phenomenon was recognised long before the birth of the oldest men now alive. Then came the famous work of Zwaardemaker, who brought order to the subject of odour counteraction and who contributed a great deal of new thought and experimental work.

### Zwaardemaker's olfactometers

If counteraction was to be investigated logically, it was obvious that some device was necessary which would enable smell to be dealt with quantitatively. Zwaardemaker designed his famous olfactometer (Fig. 1, left). The bent tube on the right of the figure is inserted directly into the nostril. When the observer breathes in, air passes through the wide tube of which the inside surface is coated with whatever odorant material is being used, and it then passes through the narrow tube to the nose. The two tubes are telescopic and the narrow one can be pushed right into the wider one so that there is none of its inner odorant-coated surface that is exposed to the inspired air. Alternatively the inner tube can be pulled out so far that almost the whole length of the odorant-coated surface is exposed to the inspired air. If the inner tube is pushed right into the outer one the air is not odorised at all; if the inner tube is pulled out of the outer one the air is thereby odorised, and the further out the inner tube is pulled the stronger is the odour of the inspired air.

The minimum perceptible concentration was designated by Zwaardemaker as an olfactie. The extent of withdrawal of the inner from the outer tube to give one olfactie was different for different odorants. Typical values were:

| | |
|---|---|
| Balsam of Tolu .. .. | 1 mm. |
| Yellow wax .. .. | 4 mm. |
| Paraffin wax .. .. | 20 mm. |

This is in line with what we might expect; balsam of Tolu has a powerful smell, paraffin wax has one that is weak. When using the olfactometer for counteraction work Zwaardemaker used two in series, one containing one odorant, the other the other odorant. Air passed through one olfactometer, into the next and then into the nose. A translation of Zwaardemaker's own description[7] of this work runs as follows:

> "It is only necessary to slide out the cylinder of one olfactometer to a certain mark, and to hold another immediately in front of it, so that the air from the first passes into the second. Then the definitely measured amounts of each separate odour are inspired; these mix in the apparatus as well as in the nose." And later: "According as one or the other sensation predominates either the one or the other smell is noticed, *and when they are exactly counterbalanced, then either no precise sensation is experienced, or only a very weak impression, quite indefinite, which was noticeable only by great effort and corresponded with neither of the componenis.*"

The italics are ours because this is really the crux of the matter. Pairs that Zwaardemaker discovered and the relative proportions in which they gave complete counteraction were as follows:

2¾ olfacties cedarwood and 14 olfacties indiarubber
3½ olfacties benzoin and 10 olfacties indiarubber
8½ olfacties paraffin and 14 olfacties indiarubber
14 olfacties indiarubber and 28 olfacties wax
14 olfacties indiarubber and 70 olfacties balsam of Tolu

Experimentally one olfactometer containing *e.g.* benzoin is placed in front of another containing indiarubber. The two odorants mix in the second olfactometer and also in the nose and give complete neutralisation.

Zwaardemaker thought that mixing of the two odorants in the olfactometer might be open to the objection that the two odorants would be in contact in the second of the two olfactometers and that they might react chemically therein. The likelihood of this was not as a rule very great, but nevertheless to avoid the objection Zwaardemaker designed his double olfactometer (Fig. 1, right); the two side-by-side tubes each contain one of the pair of odorants and each is inserted into a nostril. A translation (our italics) of what Zwaardemaker[8] wrote is:

> "It is very simple to convince oneself qualitatively that even with the double olfactometer two sensations can neutralise each other. . . . Experiments can be made with quite strong stimuli without producing a mixed smell sensation. One or the other smell will usually predominate to a greater or lesser degree, but *if the right conditions are finally found, then there will be no trace of any smell. The elimination of smell sensation is then absolute.* Nevertheless there is not the slightest doubt that the two odours normally would separately have an effect on the sense-organ."

### Pairs of industrial importance

In later papers Zwaardemaker[9] discussed pairs of counteracting odorants, of which one member of the pair was really objectionable. Some of these frequently occur in industrial effluents today, notably the mercaptans. Pairs thus referred to were: ethyl mercaptan (rotting cabbage and sewage smell) counteracted by (*a*) coumarin (new-mown hay smell) or (*b*) caproic acid (goat-like) or (*c*) by eucalyptol; skatole (fæces smell) counteracted by coumarin.

### Confirmation of Zwaardemaker's work

Work recently carried out and reported by the author[10] has confirmed the main findings of the earlier work. The sort of result obtained is that when two odorous airs are mixed, one odorised with butyric acid, the other with oil of juniper, then, if the proportions are suitable, the mixed air will smell neither of butyric acid nor of oil of juniper, but will have a soft unidentifiable smell, not strong but quite slight. The author has not found conditions of "no odour" resulting from mixing two odorous airs, and this is a bit at odds with Zwaardemaker's findings, but very many pairs have been found which when mixed give only a slight unrecognisable odour. The conclusions drawn from this later work point to the existence of effective counteractants for most classes of malodours likely to be encountered in industry.

### Industrial odours

For a long time there was a great temptation to ignore unpleasant industrial odours. Factory managements would do their best to keep them down, but often it was impossible to carry on a chemical process, one such as the manufacture of chlorphenols, without odorising the neighbouring air. At a time when neither factory management nor Public Health authorities nor anyone else knew how to reduce the odour short of shutting down the manufacturing process, it was best to ignore it as much as one could. The people who lived in the vicinity often derived part of their livelihood, either directly as salary or wages, or indirectly as local traders, from the presence of the factory and were generally unwilling to do anything to embarrass its continued operation.

All that has changed and today there are specialists only too anxious to clear up anybody's odour trouble. The general remedial measures at their command will be briefly outlined and then particular attention will be given to the counteraction of industrial odours; for this is the newest and in many ways the most interesting of all the methods available.

### Location

If a factory is already built and operating not much can be done about its location. If it is not yet built, then it is only sensible to think about the effluents and the effect they are going to have on the district.

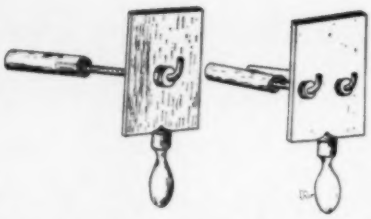

**Fig. 1. Zwaardemaker's single (left) and double (right) olfactometers.**

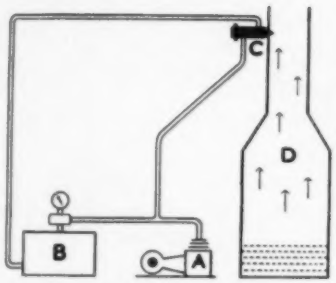


**Fig. 2. Diagram illustrating the principle of injecting counteractant. A, compressor; B, counteractant reservoir; C, spray gun; D, malodorous stack or vent.**

**Fig. 3. Enlarged view of air spray gun through which counteractant is applied. (Courtesy of Airkem Inc.)**

Within the last few months a mushroom farm down in Sussex was giving offence to local residents by the smell from the stacked horse dung. After a good deal of consideration it was thought simplest to move the farm to a new and more remote site, and this was done. Doubtless to the farmer this seemed difficult enough, but moving a factory might well provide problems of a different calibre. Another odour nuisance that was really due to bad siting was at Merano, a beautiful locality with a good climate and noted for the sanatoria near to it. There, in a small side valley, there was opened a factory for the production of synthetic ammonia, and the patients at the sanatoria started to feel ill when they saw the typical yellow-brownish haze of nitrous gases coming out of the smoke stack. Apparently they received little sympathy from the technicians at the factory who were inclined to laugh their complaints to scorn. This and other examples of bad siting were discussed at the First International Congress on Air Pollution held in New York in 1955; some of these examples were later reported by the author,[11] who attended the Conference.

### Methods of odour suppression

**Combustion** is one of the best-known, and where it is applicable probably the best of all processes. If the offensive odorous gases can be burnt in a furnace to carbon dioxide, then that is the end of the matter as a rule; there may be a little sulphur dioxide formed if the original odorants contained sulphur, but, except in relatively large quantities, sulphur dioxide is not very objectionable or toxic. Care must be taken to effect complete oxidation because incompletely oxidised products, for example aldehydes, can be worse than the original odorant. When the odorant material is present, as it often is, in only a very small proportion in a large volume of air, combustion is not practicable. If the odorant is not too dilute combustion can be a good method and the American Petroleum Institute have stated[12] that "the best method for the ultimate disposal of all combustible odorous compounds occurring in the refinery is high-temperature oxidation. The principal products of combustion are $CO_2$, water and $SO_2$; these are discharged from the top of high stacks." But if there is a lot of air and a very little odorant it is not going to be economically practicable to heat up all the air in order to burn up the little bit of odorant.

**Absorption** of odorants by acids, alkalis and hypochlorites has long been practised; the method is particularly applicable if the odour is due to bacterial action and if the hypochlorite can be applied to the odour source where it will kill the bacteria.

**Adsorption** on active carbon is a good method of removing odours from air; it is most suitable when the air is fairly rich in odorant. Installation of a carbon adsorption plant is costly, and furthermore the

carbon has to be revivified frequently by steaming out whatever has been adsorbed and then drying the clean but wet carbon. In general, carbon adsorption is worth while only when it is required to recover the odorant that has been adsorbed, as distinct from disposing of it.

**Ultra-violet irradiation** is sometimes used for deodorisation; it can be very effective in closed compartments that are used, for example, for the storage of meat. The radiation from ultra-violet lamps is bactericidal and so kills some odours at source, but the main deodorising action of U.V. lamps is due to the traces of ozone that they generate. Ozone is very toxic and care has to be taken that its concentration does not rise above a level that is very low indeed. If the rooms in which U.V. lamps are used are inhabited (as distinct from store-rooms that are entered only occasionally and for short periods of time), very great care is necessary to avoid the incidence of a toxic concentration of ozone.

**Masking** has been defined by McCord and Witheridge[13] as " the process of obliterating one odour by superimposing another to create a more compelling sensation, preferably pleasant." It is a process that often finds employment in overcoming household smells; indeed, many of the floral aerosols act mainly by masking, but the dissemination of a new and probably unwanted odour over a large area that may surround a factory would not be so good; neither as a rule would the imposition on manufactured articles of such a powerful smell as was necessary to overcome an unpleasant odour inherent in the articles themselves.

**Fig. 5. Odour counteractant being sprayed at an American sewage farm. The container is the drum in which delivery of counteractant is made. (Courtesy of Airkem Inc.)**

## Counteraction in industry

Industrial odour counteraction has grown enormously in the last 10 or 12 years; there are specialist organisations that will survey, usually without charge, an odour problem—*e.g.* a sewage farm or factory with an offensive effluent—and will prepare a plan to overcome the odour trouble. Usually this will include a recommendation to install a simple spraying equipment, the principle of which is shown in Fig. 2. An enlarged view of the air-spray nozzle through which the counteractant is applied is shown in Fig. 3. This installation is by no means costly and if a compressed-air line is already available the cost can be trivial; if compressed air is not available the installation of the necessary compressor will be the most expensive item. A chart showing the optimum rate of use of counteractant, similar to Fig. 4, may also be provided.

## Sewage farms

Sewage practice has changed over the last 15 years because of the rapid growth in the use of synthetic detergents. At one time the soap in the raw sewage could be cracked by adding acid and the fatty acids precipitated. The synthetic detergents are stable in acid solution and they have imposed new demands on the sewage technicians. The new conditions have been satisfactorily met, but whenever there are changes in the industrial processes that are carried on in the district, the load at the sewage farm may change and new odour problems may arise. Even when everything is going well, even when the effluent from the sewage farm is so good that fish will live in it, there is usually an unpleasant even if not a strong smell in the neighbourhood of sewage works. If everything is satisfactory and still an odour persists, that is the time for the counteraction method to be used; it is important not to use it to cover up bad operation and toxic conditions. Treatment consists of vaporising the counteractant, which is a liquid, through spray nozzles, the vapour of the counteractant neutralising the sewage odour and reducing the

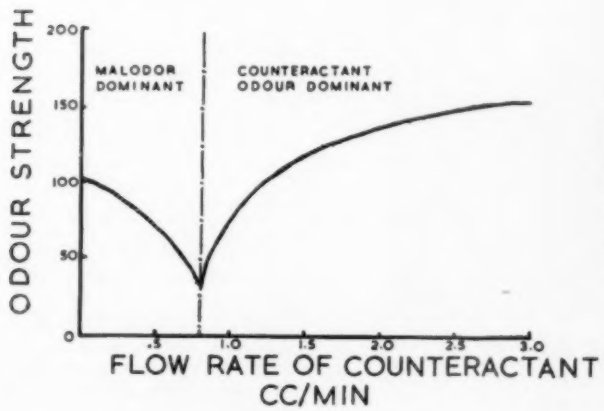


**Fig. 4. Graph showing optimum neutralisation point corresponding to the most favourable dose of odour counteractant.**

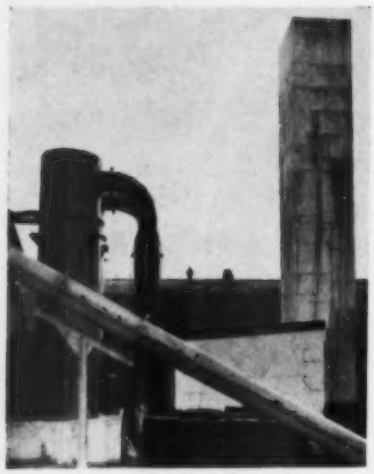

**Fig. 6. Plant at the Herring Board's factory at Stornoway. The condensers are on the left and the ducts leading from them are treated with counteractant before the gaseous effluent reaches the stack. (Courtesy of Airwick Ltd.)**

total odour level. Fig. 5 shows equipment in use at an American sewage farm. Counteraction of sewage odours has been described in some detail by Post.[14]

### Fat rendering

According to von Bergen,[15] who was successful in counteracting the odours from some rendering plants, the likely sources of odour in such plants are many and he instances: loading platforms, cookers, blood dryers, presses, the hides themselves, and others. Many of the offensive odours are ammoniacal, notably ammonia itself, mono- and dimethylamine and ethylamine; others are sulphurous, notably hydrogen sulphide and traces of mercaptans. If the flesh or fish that is being used as the raw material is stale instead of fresh, then the odour troubles are much worse because the quantities of amines released may be ten times as great as when fresh flesh is used.

Von Bergen recommends a three-step method of treatment:

(1) Odour counteractant should be vaporised into the stacks which carry off the effluent from the cookers and the dryers.

(2) The buildings should be kept under negative pressure so that when a door or window is opened fresh air flows into the building, and so that malodorous air cannot escape through window or door but must escape through the vent into which it is drawn by a fan, and where it can be sprayed with counteractant.

(3) Good sanitation and cleanliness must be maintained. Odour counteraction should not be regarded as a substitute for good housekeeping.

### Fish products

The Herring Industry Board has a factory at Stornoway in the Isle of Lewis where herring brought in by a large fishing fleet are reduced to obtain an edible oil and animal food. The factory has been successful, but at first it gave a good deal of trouble with an effluent odour which made the neighbourhood unpleasant. Conventional methods of treatment were first tried, namely:

(1) Part of the malodorous air was passed through the firebeds of the boilers, to burn the odorant matter.
(2) Scrubbing.
(3) Chlorination.

The results were not completely satisfactory and the air discharged from the stack was malodorous. The odour was found to emanate from the dryers, whence it passed through a pair of condensers (Fig. 6) and thence to the stack. The spray gun which was used to inject counteractant is shown (Fig. 7) in the ducting leading from the condensers. Application of the counteractant was successful in overcoming the nuisance.

Another example is provided by the Nassau Fertilizer and Oil Co. who had excessive trouble with the smell of fish solubles.[16]

**Fig. 7. Enlarged view of the ducts in Fig. 6 showing the counteractant spray gun in position. (Courtesy of Airwick Ltd.)**

### Paper factories

There can be many odour sources in a mill that converts wood to pulp and paper. According to von Bergen[17] the worst trouble spots are the digester blow-off stacks or vents both during the relief of digesters while cooking and also during the blow-down of pressure prior to and during the discharge of pulp. Treatment is the same in principle as that outlined for the other odour nuisances: the source of the odour is diagnosed, a suitable counteractant is built up and supplied by a specialist firm, and it is sprayed into the malodorous effluent. The largest paper mill in Texas used this method with advantage and to the improvement of good-neighbour relations with the local people.

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## Crystallisation

*By J. W. Mullin. Butterworths Publications. London*, 1961. *Pp.* 268, *illus.* 60*s. net.*

In spite of its great importance in industry, very little information has been published on what may be termed the practical side of crystallisation—considerable knowledge and experience being retained by comparatively few people inside the industries. Certainly no publication in the English language has previously appeared which has been devoted to the survey of all aspects of crystallisation practice. The publication of Prof. Mullin's work remedies the omission.

Much material has already been published on the specialised subject of crystalline state and crystallography, and in his first chapter the author rightly confines himself to a brief introduction on the subject. The short bibliography for recommended study is adequate.

Chapters 2, 3 and 4 deal with solutions and solubility, the fundamental physical and thermal data on which crystallisation depends, and phase equilibria. Explanations are clear and precise and useful information is given. However, these subjects are of prime importance to the designer and reference to I.C.T.,[1] Kirk-Othmer[2] and that most comprehensive of all works on solubility—Seidell[3]—may well have been made. In industrial practice pure solutions are the exception rather than the rule and it is felt that greater emphasis may have been made on this point.

The effect of impurities, existent or added, of surface-active agents, of *p*H, of viscosity and temperature upon the growth rate and habit of the crystal can be most pronounced. The aspect of crystal growth giving rise to hard scale formation which is often most troublesome and one of the nightmares of the crystalliser designer and operator is important. More information on this subject in Chapter 5 on the "Mechanism of Crystallisation" could have been usefully added, albeit in a general way. The complexity of the variables involved in the crystallisation process makes anything but broad comment impossible and is probably the major reason for the scarcity of published data on practical applied crystallisation and for such data as are published being related to a specific substance being crystallised.

Crystallisation as practised in industry and the type of crystallisation equipment employed are amply dealt with in Chapters 7 and 8.

Prof. Mullin concludes with Chapter 9 on the subject of size grading of crystals and gives emphasis to the importance of uniform particle size as the criterion of good crystalliser design. In industrial practice, crystallisation does not end with making of crystals in the crystalliser. The crystals must first be separated from their mother liquors and frequently dried and stored. Too frequently uniform and attractive coarse crystals produced by a crystalliser are broken and spoilt, soft friable crystals are disintegrated, and small crystals cannot be separated from the liquors because the wrong type of dewatering equipment, drier or conveyor has been used. Whilst dewatering, drying, conveyance and storage are separate unit processes they are so closely allied to that of crystallisation that some reference should have been made generally on these subjects.

Useful tables on solubility and heats of solutions are given in the appendix.

Criticism can only be of omissions. Within the space available, Prof. Mullin has successfully achieved his aim of presenting crystallisation as a unit operation. Whilst crystallisation, because of the very complexity of the subject, must remain very much an art, the author has shown where science emerges. The book is not only concise, but is presented in an easily readable manner which should make it doubly attractive and of value not only to students of chemical engineering but to the process chemist and chemical engineer.

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A. W. Bamforth.

## Letters to Salesmen

*By Stuart Thomson. The World's Work (1913) Ltd., Kingswood, Surrey.* 1961. *Pp.* 189. 18*s. net.*

British businessmen are gradually realising that salesmen are V.I.P.s. However good a product may be and however keenly it may be priced, it is a dead loss unless it can be sold. This book is a distillation of the techniques the author has used in 25 years of selling. It is written in the form of brief letters, each dealing sympathetically and sensibly with the difficulties the salesmen face every day. A few of the titles of the letters give the essence of the style and content: Sell for selling's sake; It's in the bag; It pays to be partial; It's evening in the provinces; "I have a wife and children to feed."

Mr. Thomson writes easily and clearly and puts over his abundant common sense with a simple directness that is most appealing. The sales manager will find in the book much shrewd advice that he would probably have liked to have thought of first. The salesman will find a deep understanding of his problems. Everyone who works in the hard day-to-day business of selling will benefit from this book. Managements should make sure their salesmen read it thoroughly.

Mr. Thomson makes generous acknowledgment to the guidance he received in his early years from Leonard Hill, chairman of the proprietors of Manufacturing Chemist. From his association with publishing he acquired not only much of the technique of selling he so ably expounds, but also an attractive writing style.

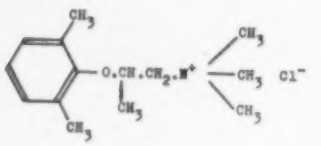
# THERAPEUTICS

By S. J. Hopkins, F.P.S.

*Cardio-vascular therapy · Controlling appetite · New methods of controlling fungal infections · Cytostatics · Colchicinic acid derivative for gout · Morphine adjuvant · Analgesic effect of cold*

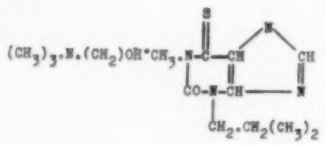
## Cardio-vascular drugs

A COMPOUND with an action similar in effect to that produced by ganglionic blockade has been described by Rowe[1] *et al.* The substance is the β-methyl-2.6-dimethyl-phenyl-ether of choline, (1) and the hæmodynamic action is ascribed to the effects of the drug in blocking the release of catecholamines from nerve endings. This results in a decrease in cardiac output, but although the coronary blood flow is reduced, the oxygen consumption of the myocardium is maintained.



(1)

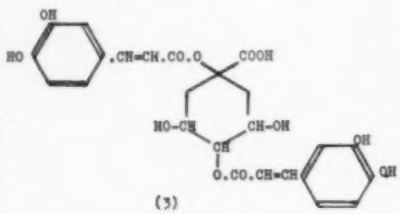
A new series of broncho-coronary dilators of the thioxanthine group is also referred to by Armitage[2] and Wooldridge. Theophylline (widely used as aminophylline) is 1 : 3-dimethylxanthine, and can be converted easily to the corresponding 6-thio-derivative. The choline salt of this thio-derivative is more active than choline theophyllinate, and in consequence a series of 1-3-dialkyl-6-thioxanthines were examined. The differences were mainly quantitative, the most effective compound being the choline derivative of 3-*iso*-butyl-1-methyl-thioxanthine (2). This compound is also referred to by Armitage[3] *et al.*, who consider it to have a more powerful coronary and broncho-dilator action than theophylline, but to be less effective as a diuretic.



(2)

Rowe[4] and others also report on the coronary activity of 1-(2-methoxyphenyl) - 4 - (3 - methoxypropyl)-piperazine phosphate (also referred to as Ansiv). This compound may be of clinical interest if further work confirms preliminary findings.

A number of hydrazine-derived inhibitors of monoamine oxidase have certain applications in hypertension, but a new inhibitor, not derived from hydrazine, and also possessing hypotensive properties, has been referred to by Horwitz[5] and Sjoerdsma. This compound, also described by Taylor[6] *et al.*, is N - benzyl - N - methyl - 2 - propylamine hydrochloride, and was given in single daily doses of 75-125 mg. At this dosage level the drug had a sustained action on the blood pressure without causing tachycardia. The effect is regarded as being mediated via the sympathetic nervous system, and the authors consider that an extensive clinical trial of the drug is indicated.



(3)

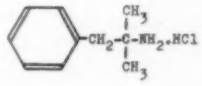
Interest in atherosclerosis continues, and Cynarin, the active principle of artichoke, has been investigated from this point of view by Mancini[7] *et al.* (3). The use of cynarin in this way was first suggested by Eck[8] and Desbordes, and the compound was synthesised and examined pharmacologically by Preziosi[9] and Loscalzo. Clinical trials in a series of 23 patients with atherosclerosis, using doses of 250 mg. thrice daily, indicated that the drug could bring about a definite fall in blood-cholesterol levels. The average reduction achieved after eight weeks treatment was about 25%, and of significance is that not only was an absolute reduction obtained, but that much of the fall was in β-cholesterol levels. The mechanism is not clear, but part of the reduction in cholesterol blood-level is due to increased excretion by the bile, and probably by an increased conversion of the cholesterol to bile acids. The drug is well tolerated, and a wider clinical examination of its therapeutic value may be worth while.

Experimental studies by Karczmar[10] *et al.* on the possible value of amotriphene in angina pectoris and cardiac arhythmias have been confirmed by Harris,[11] and more recently by Brown[12] *et al.* The drug, also known as Myordil or 3-dimethylamino-1.1.2-*tris*-(4-methoxyphenyl)-1-propene hydrochloride, has twice the coronary dilator power of papaverine, and more than four times the activity of quinidine or procaine amide in checking auricular fibrillation and other cardiac arhythmias. This action is not accompanied by myocardial stimulation, and the drug thus possesses a therapeutically valuable pattern of activity.

## Appetite control

The earlier drugs used to control appetite, represented by dexamphetamine, appear to exert their effects in part at least by a central stimulation. This is often undesirable, and Holm[13] *et al.* have sought for other compounds, reasoning that, as some stimulants such as caffeine and methyl phenedate do not affect appetite, some appetite suppressant without any central stimulant action might be found. A series of nuclear

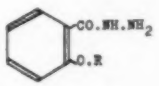
substituted phenyl $\alpha$ methylamines was studied, and several were found to have anorexic properties. The most effective compound (4) had the following structure, and the $\alpha$ chloro and *p*-bromo compounds were also active. Substitution with hydroxyl, methyl or methoxy groups resulted in loss of appetite-depressant activity. The active compounds lack the motor-stimulant properties of the amphetamines, so that separation of the two types of action appears to be practicable.



(4)

**Anti-fungal agents**

The apparent resistance of fungi to therapeutic attack has long been a clinical problem, but a new method of potential value has been suggested by Thu-Cuc[14] *et al.* These workers noted the close relationship between mycobacteria and fungi represented by Actinomycetales, and therefore tried out tuberculostatic compounds as anti-fungal agents. Some compounds, such as isoniazid, which have antifungal properties, also have heavy metal chelating powers, and new and more active substances were therefore sought in other hydrazine derivatives, particularly the benzhydrazides. Examples of the compounds studied include *o*-alkoxybenzhydrazides; (5) 2-hydroxy-4-alkoxy benzhydrazides (6) and the 2-hydroxy-5 alkoxy-derivatives.



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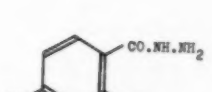
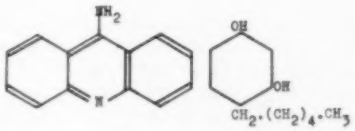


(6)

Methods of synthesis are described, and both the 2-hydroxy-4-alkoxy and the corresponding 2-5 compound were particularly active when tested against *Candida*.

Fungal infections of the urinary tract have become more common since the introduction of the broad spectrum antibiotics, and Goldman[15] *et al.* report favourably on the use of amphotericin B in monilial cystitis. This condition is not easy to treat, and although *Candida albicans* was once thought to be the only pathogenic organism of that group, it is now considered that others may be concerned in moniliasis. In cases not responding to standard therapy, Goldman found bladder instillations of amphotericin B, in doses of 15 mg. per 100 c.c. of water daily, to be effective. These instillations were associated with the administration of an alkalising mixture, on the assumption that an alkaline urine inhibits monilial growth.

*Pityriasis versicolour* is a fungal infection of a less serious character, easily diagnosed, resistant to treatment, and a burden to both patient and doctor. Zimmerman,[16] however, has obtained good results with 9-amino-acridinium-4-hexylresorcinolate (7).

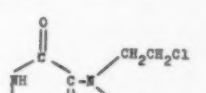


(7)

This compound was used as a 0·2% solution in propylene glycol, as an ointment and as an aerosol spray. In the majority of 39 patients, complete elimination of the fungus, both clinically and microscopically, was achieved within 4-8 weeks. The acceptability and efficiency of the product appears to be exceptional. The author points out that re-infection may occur, as host susceptibility varies widely, but such re-infections also respond readily to treatment.

**Cytostatics**

The use of carriers for alkylating agents such as chlorambucil has a number of interesting potentialities, and Shanbron *et al.*[17] report favourably on uracil-mustard (8). It is considered that some tumour cells may contain enzymes that can increase the utilisation of uracil, thymine, and such compounds may be taken up preferentially by tumour cells. If a nitrogen mustard compound is linked with uracil, an increased concentration of the drug in the tumour cells may occur. Some good results were obtained in this way with uracil mustard given orally as single daily doses of 1-2 mg., and the compound was found more effective than others for lymphoma and chronic leukæmia, and some solid tumours also responded. In some cases an exceptional degree of clearing of heavy bone marrow infiltration was noted. Work on the chemotherapy of adrenocortical cancer is the subject of a report by Bergenstal[18] *et al.* It is known that DDT (9)



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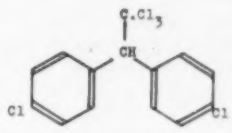

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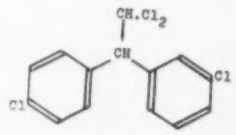


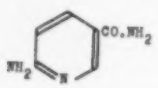
(10)

can produce a selective necrosis of the adrenal cortex, although the drug is not suitable for therapeutic use. Further investigation on similar lines indicates that a contaminant of DDT (10) was more effective. This compound had a related structure, and when given in large doses, together with anti-emetics to reduce side effects, it was found to produce regression of the tumour, and also of pulmonary and abdominal metastases. The effect of the drug is unusual inasmuch as it is effective chiefly on one type of tumour, and the neoplasms from it. The compound thus has a very valuable specific effect, and further work on the drug may be rewarding.

Disseminated malignant conditions, particularly in the late stages, are often complicated by effusion of fluid into the pleural and other cavities of the body, which can be very distressing. Levison[19] has used direct injection of nitrogen mustard solutions into the cavity in attempts to reduce the degree of

effusion, and in a series of 19 patients, improvement was found in 11. The duration of control was considerable, and the results were comparable in general with those following the use of radioactive gold (Au 198) with the advantages of reduced risk and greater ease of administration.

Herter[20] *et al.*, working on other aspects of cancer therapy, refer to 6-aminonicotinamide (11). This compound has little activity alone, but augments the cytostatic action of mercaptopurine, which is now in frequent use in the treatment of leukæmia. Aminonicotinamide is thought to be a true antimetabolite of nicotinamide, and can thus be incorporated into pyridine nucleotides. It may further inhibit enzyme reactions in which these nucleotides take part. The drug is not free from toxic side effects, but may prove a useful adjuvant to other forms of therapy.



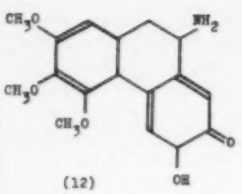
(11)

**Gout**

Colchicine has long been recognised as the specific treatment of acute gout, but in practice the toxic effects of the drug (which were known to Dioscorides) frequently limit its value. As alternatives colchicoside was found less effective, and desacetylmethylcolchicine, whilst having less gastric irritant action, may cause agranulocytosis. Wallace[21] has used the trimethyl derivative of colchicinic acid (12), and in a series of 34 patients with acute gout, 26 responded well with few side effects. The drug was given in doses similar to those of colchicine, and from a consideration of structure and activity, it is suggested that the side chain of the third ring of the colchicine nucleus is essential for adequate therapeutic activity.

**Analgesics and anaesthetics**

In the treatment of severe and intractable pain, morphine still ranks high, but the side effects of the drug often prevent the use of high doses. For this reason adjuvant compounds have long been sought, and the discovery of levallorphan and other morphine antagonists



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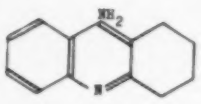


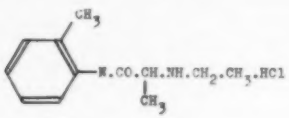
(13)

indicated that less completely effective compounds might conceivably inhibit the side effects without reducing the analgesic potency. Aminophenazole was one of the early compounds to be used in this way, but a more reliable and stable drug has been found by Stone[22] *et al.* in tetrahydroaminacrine (T.H.A.) (13). This compound is a respiratory stimulant and antinarcotic, but it does not interfere with sleep. In a series of 60 patients with severe pain, the drug enabled adequate doses of morphine to be administered without excessive side effects. No addiction was encountered, and although tolerance may develop, this is not a serious problem, and the drug has definite applications in the control of severe and continued pain.

**Analgesics**

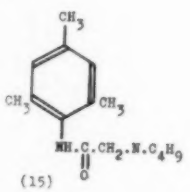
The analgesic effects of cold have long been known, but the therapeutic use and value of cold is limited. Ethyl chloride has been used in the past for the relief of sprains and myalgias, and was reported on more recently by Taverner[23] in postherpetic neuralgia. The drug is not without its dangers, as it is inflammable, and has anæsthetic and toxic properties, and Ellis[24] has investigated the value of other and inert liquids of low boiling point as cold-producing products when applied to the skin. Successful results were obtained with a mixture of fluoromethanes (available as Skefron). Applied as an aerosol spray, excellent results were obtained in a variety of conditions of acute pain associated with muscle spasm, including renal colic, dysmenorrhœa and fibrositis. The aim of treatment is not to produce anæsthesia by freezing, but to interrupt or swamp out the pain impulses by a series of cold impulses, and the technique of spray production is important.

Interest in compounds of the lignocaine type continues. Wielding,[25] and Strom[26] and Persson have examined α-n-propylamino-2-methylpropionanilide (14), and report it as being a stable compound, similar in local anæsthetic action to lignocaine. The clinical value



(14)

of the drug is limited as the action is not extended by admixture with adrenaline, which is almost a routine measure with related compounds. Work on other substituted anilides is based on the pharmacological activity of the methyl analogue of lignocaine, and Dofek[27] *et al.* have prepared a new series of substituted basic anilides, and the thio derivatives of substituted ω-aminoacetophenones. This paper discusses the influence of changes in chemical structure on anæsthetic activity, toxicity and other factors, and the high activity (tenfold) of the following compound (15) is of considerable interest:



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(*Continued on page* 378)

# *HORMONES and Related Compounds*

**By R. M. Evans,*** D.Sc., F.R.I.C.

*Further progress in polypeptide synthesis · Melanocyte-stimulating hormones · Structure of ribonuclease elucidated*

## POLYPEPTIDES

SEVERAL recent advances in the synthesis of biologically active oligo- and poly-peptides were described in the previous review,[1] and here I shall consider further developments in this field. The rapid progress being achieved in the synthesis of increasingly complex polypeptides has been made possible by the discovery and development of highly efficient methods for forming peptide linkages and elegant means for protecting other active centres in the molecules. It is relevant therefore to review briefly the recent improvements in these techniques.

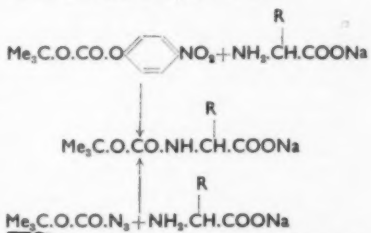
The fundamental problem in peptide syntheses is to produce the desired amide link between two amino acids without inducing racemisation, and the effective blockade of alternative reactive groups is a prerequisite to success. The essential features of the reaction are illustrated by the following scheme.

$$R^1CH(NHR^2).COOH + NH_2CH(R^3).COOR^4 \longrightarrow R^1CH(NHR^2).CO.NH.CH(R^3).COOR^4$$

The protecting groups $R^2$ and $R^4$, which prevent reaction of the alternative amino and carboxyl groups, must be easily introduced and readily removed without damage to the peptide. Some amino acids also contain hydroxyl or thiol groups, and these also may have to be protected.

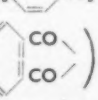
### The protection of amino, hydroxyl and thiol groups

The use of benzyl ($Ph.CH_2$—) and benzyloxycarbonyl ($Ph.CH_2.O.CO$—) derivatives for the protection of amino, hydroxyl or thiol groups is well known;[2] both groups are readily removed by reductive methods. More recent additions to the armamentarium are the *tert.* butyloxycarbonyl derivatives, readily formed by the reaction of the sodium salts of amino acids with *tert.* butyl *p*-nitrophenyl carbonate or azido *tert.* butyl formate.[3]



Unlike the corresponding benzyloxy derivatives, the *tert.* butyloxycarbonyl derivatives are stable to reduction but readily removed by acid hydrolysis, when they give rise to gaseous by-products, thereby simplifying greatly the purification of the product.

$$Me_3C.O.CO.NH.CH(R).CO.NH.R^2 \xrightarrow{H^+} NH_2.CH(R).CO.NH.R^2 + Me_2C{=}CH_2 + CO_2$$

The tosyl ($CH_3C_6H_4SO_2$—) and the phthaloyl  groups are also extensively used to protect amino groups. The former is readily removed by sodium in liquid ammonia[4] and the latter by treatment with hydrazine.

### The protection of carboxyl groups

The carboxyl groups of peptides and amino-acids are protected most frequently by esterification. Methyl and ethyl esters, although widely used, have shortcomings: they react readily with hydrazine, and the aqueous acid conditions necessary for their hydrolysis may rupture peptide bonds or remove other protecting groups. In contrast the *tert.* butyl esters, which are readily prepared by reaction of the acid with isobutylene, do not react with hydrazine and may be hydrolysed under anhydrous conditions.[2]

$$R.NH.CH(R^1).COOH + Me_2C{=}CH_2 \rightleftharpoons R.NH.CH(R^1).CO.O.CMe_3 \quad (H^+)$$

### Selection of protecting groups

Considerable art lies in choosing protecting groups that will remain in combination during the synthesis until the appropriate point for their removal. In a recent excellent review Anderson[2] recommends

(*a*) the use of benzyl, tosyl or benzyloxycarbonyl derivatives when protection is required until the end of the synthesis;
(*b*) the use of *tert.* butoxycarbonyl or benzyloxycarbonyl derivatives for temporary protection; and
(*c*) the use of *tert.* butyl esters for the temporary protection of esters during the synthesis.

### Formation of the peptide bond

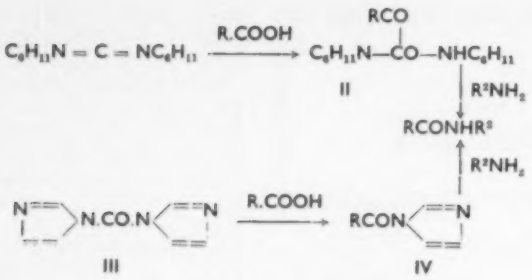
The formation of the peptide bond between suitably protected amino-acids is usually aided by forming a reactive derivative of the carboxyl group as indicated below.

$$RCH(NHR^1).COX + NH_2CH(R^3).COOR^2 \longrightarrow RCH(NHR^1).CO.NH.CH(R^3).COOR^2$$

Well-known methods are the formation of the azide ($X = -N_3$)[5] or the mixed carbethoxy anhydride ($X = -O.COOEt$).[6] More recent innovations have been the use of di*cyclo*hexyl carbodiimide (I)[7] and of dicarbonyl diimidazole (III).[8] The former reacts with carboxylic acids to form acyl ureas (II) and the latter gives rise to acylimidazoles (IV): both the intermediates react readily with $\alpha$-amino groups to form the required peptides.

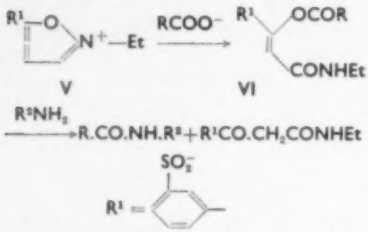
The nitrophenyl ($-CO.OC_6H_4NO_2$) esters are also highly effective, and their usefulness has been clearly demonstrated by du Vigneaud and Bodansky in the synthesis of oxy-

* Glaxo Laboratories Ltd.




tocin,[8] and by Schwyzer and his co-workers in the preparation of gramicidin S.[9]

Finally we have the discovery, announced by Woodward and his colleagues[10] this year, that carboxylates react with 3-unsubstituted isoxazolium salts (V) under mild conditions to give enol esters (VI), and these with α-amino groups form peptide linkages efficiently with little racemisation.




The perfect condensing agent has still to be discovered, but many of the methods described can give yields of *ca.* 90%; the stepwise syntheses of octa- and nona-peptides have been achieved with over 50% yields.[11]

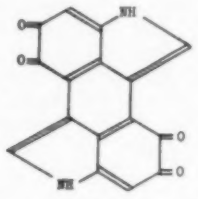
## THE MELANOCYTE-STIMULATING HORMONES

The work on the structure and synthesis of the melanocyte-stimulating hormones, brought to fruition in the past five years, constitutes a significant advance in our knowledge of the polypeptide hormones.

The presence in the mammalian pituitary gland of a substance that caused darkening of frogs' skins was noted over 30 years ago. It was not, however, until 1956 that Lerner and Lee[12] established that two different polypeptides, which they named the α- and β-melanocyte-stimulating hormones (α- and β-MSH), were responsible for this phenomenon. The two polypeptides, obtained from pig pituitary glands, showed different characteristics, α-MSH having basic (iso-electric point 11·0-11·5) and β-MSH acidic characteristics (iso-electric point 5·2-5·8).

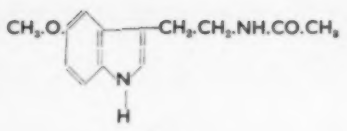
### Melanocyte cells

The changes in the colour of amphibia induced by these hormones have been studied extensively, and it has been found that their melanocyte (pigment) cells contain granular melanin[13] (VII), an indole pigment. Under the influence of α- or β-MSH the melanin granules are dispersed throughout the cell, causing the skin to appear dark in colour. This action can be blocked or reversed by a number of agents, including hydrocortisone, tri-iodothyronine, acetylcholine and melatonin,[14] which, in contrast to α- and β-MSH, cause aggregation of the melanin granules and a consequent lightening in skin colour (see Fig. 1 reproduced by courtesy of *Nature*).




VII

Melatonin is the most potent of the MSH antagonists, being $10^5$ times more active than any of the other inhibitors. It was first isolated in 1958 from bovine pineal glands and obtained crystalline a year later.[15] Melatonin has been proved by degradation and synthesis to be N - acetyl - 5 - methoxytryptamine (VIII),[15] a derivative of the ubiquitous 5-hydroxytryptamine.




VIII

Both α- and β-MSH are extremely potent substances, $10^{-8}$g. being sufficient to turn a pale frog dark.[16] Administration of MSH preparations to man also leads to increased pigmentation, and the darkening of the skin characteristic of Addison's disease may be due to the high levels of MSH in the blood associated with this condition. The fundamental functions of α- and β-MSH in mammals are, however, not understood.[16]

### Structures of α- and β-MSH

Once the α- and β-melanocyte-stimulating hormones had been purified,[12] application of the now classical techniques for polypeptide degradation, by proteolytic enzymes or by chemical means or by both, led rapidly to establishment of their structures.

α-MSH was found to possess the same amino acid sequence as the N-terminal tridecapeptide segment of ACTH[17] and to be an N-acetyl-tridecapeptide amide. In contrast, β-MSH proved to be a linear octadecapeptide,[18] in which only the sequence of the seven amino acids 7-13 coincided with that found in α-MSH and ACTH.

In spite of the differences in their structures, α- and β-MSH have approximately equal melanocyte-stimulating potency, and it has been found that the amino acid sequences essential to activity are from acids 2 to 12 in α-MSH and 5 to 15 in β-MSH. Although ACTH contains the complete amino-acid sequence of α-MSH, it has only one hundredth of its melanocyte-stimulating activity.[19]

### Synthesis of α-MSH

The synthesis of α-MSH has been described by Boissonnas and co-

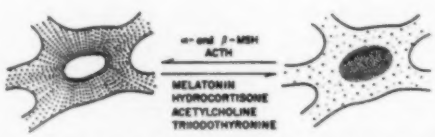



**Fig. 1. Blocking of skin darkening action of α- or β-MSH (melanocyte-stimulating hormone).**

**Fig. 2. The structures of the α- and β-melanocyte-stimulating hormones. All the acids belong to the L-series and the common sequence is indicated by the dotted lines.**

workers[20] and by Hofmann and colleagues.[21] Both routes are elegant examples of the art and science of polypeptide syntheses. The order of the steps and the methods used by Hofmann to form the amide linkages are shown in Fig. 3.

Although the products prepared by Boissonnas' and Hofmann's groups were found to be highly active, they differed in stability, and this anomaly has not been resolved.

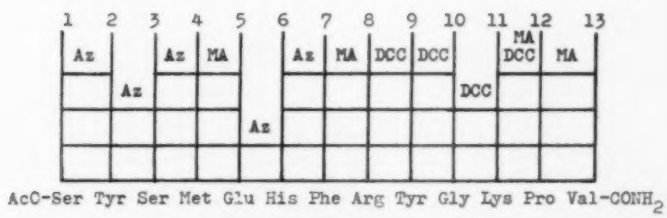



**Fig. 3. Az = Azide method, MA = Mixed anhydride method, DCC = Dicyclohexyl carbodiimide method.**

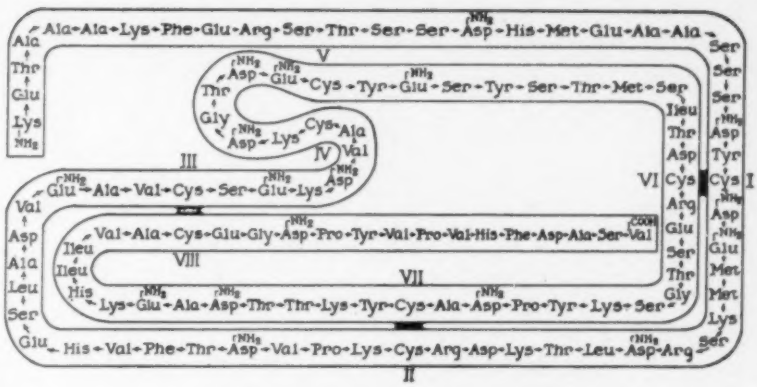



**Fig. 4. Structure of ribonuclease.**

## RIBONUCLEASE

Advances in the determination of the structure of polypeptides has recently reached a new pinnacle of achievement in the elucidation of the structure of ribonuclease. This crystalline enzyme, isolated from extracts of bovine pancreas, has a molecular weight of approximately 14,000 (*i.e.* roughly twice that of the insulin monomer). The elegant and painstaking work that led to the determination of its structure has been recently described by Hirs.[22] It has been shown to comprise 124 amino acids residues, the resulting chain being linked at four points by cysteine-cysteine disulphide bonds.

### Diagrammatic representation

A diagrammatic representation of the structure due to Spackman, Stein and Moor[23] is shown in Fig. 4 by permission of the *Journal of Biological Chemistry*.

The two-dimensional representation of such complex biologically active compounds is clearly inadequate, and study of the three-dimensional structure by physical methods is also progressing. From these combined studies we may in time learn something of the mode and selectivity of enzyme and hormone action.

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# American Commentary

NEWS AND VIEWS OF THE U.S. PHARMACEUTICAL INDUSTRY **by Dr. Rudolf Seiden**

*" Rejuvenator " banned ★ Cost of research ★ New drugs ★ Medical aerosols ★ Vitamin consumption Toilet Goods Association convention ★ Folic acid hazard ★ Animal disease laboratory*

**H.3 banned**

A Federal District Court order, on request of the FDA, has now forbidden the marketing of H.3, the " rejuvenator " which originated in Roumania and was highly publicised in Europe and America.

H.3 is claimed to be an effective treatment for " pathological ageing, nervous disorders, lack of muscular strength, lapses of memory, lack of pigmented hair, arthritic joints, arteriosclerosis, ulcers, bronchial asthma, lumbago, mental trouble, and other diseases of old age."

Dr. Ana Aslan of the Parhon Institute of Geriatrics in Bucharest, the inventor of the treatment, reported in Iron Curtain literature that 99·98% of some 8,000 old persons were revitalised by H.3, a solution containing procaine hydrochloride and a preservative. The FDA has now stopped the spreading of her disproved theory in the U.S.A.

**Cost of drug research**

According to a compilation of official and industry data the cost of research in America's drug industry has increased from $27 million or 3% of the total drug sales (of $915 million) in 1947 to $215 million or 7·6% of total sales (of $2,827 million) in 1960.

**New drugs**

The following drugs and new drug uses have been announced:

*Colymycin*, or colistamethate sodium, an antibiotic for intra-muscular use (Warner-Chilcott);

*Madribon*, or sulphadimethoxine, for the oral treatment of dermatosis (Roche);

*Mo-911*, or *N*-benzyl-*N*-methyl-2-propynylamine hydrochloride for use in hypertension (Abbott);

*Monase*, or etryptamine acetate, a monoamine oxidase used to inhibit depression (Upjohn);

*Nilevar*, or norethandrolene, a protein-type steroid (Searle);

*Synalar*, or fluocinolone acetonide, a steroid for topical application (Syntex);

*Tindal*, or acetophenazine dimaleate, for cardio-vascular patients (Schering);

*Trepidone*, or mephenoxalone, for treating anxiety (Lederle);

*Wilpo*, or phenyl-tertiary-butylamine hydrochloride, an appetite depressant (Dorsey).

*5-Fu*, or 5-fluoro-uracil, and its derivative, *5-Fudr*, are anti-metabolites (Hoffman-LaRoche) which have been used in the Cancer Research Hospital of the University of Wisconsin on a number of patients, keeping them alive up to over four years by stopping the formation of cancer cells in certain cases of cancer of the colon.

*Methotrexate*, used experimentally by Government researchers, has been declared to be the first drug which has *cured* cancer in man; the type of cancer in question originates in the membranes of the womb of pregnant women and has been considered fatal in the past. The cancer cure was announced by the U.S. Surgeon-General, Dr. L. Terry.

*2 - Methyl - 7 - chloro - 1,2,4 - benzothiadiazine - 1, 1 - dioxide* (Schering) is a recently patented drug (U.S.P. No. 2,986,573) used orally for the control of hypertension.

*Prodox*, a synthetic progesterone (Upjohn), is now recommended for suppressing heat in bitches.

*Pyridoxine*, or vitamin $B_6$, was found to reduce tooth decay if added to the daily diet, report researchers of the University of the New York Down-State Medical Centre.

**Medical aerosols**

Industry circles estimate that the aerosol output has increased over 50% during the last two years. The numbers of units of medicals and pharmaceuticals (fungicides, burn treatments, topical antiseptics, oral medicinals, anæsthetics, antibiotics, etc.) produced in the U.S. were as follows:

| | |
|---|---|
| 1958 .. .. .. | 7,129,608 |
| 1959 .. .. .. | 10,036,312 |
| 1960 .. .. .. | 11,776,836 |

**Big vitamin consumption**

The 1960 retail sales of vitamins in the U.S.A. are estimated to have reached $525 million, which averages $2·92 per person per year. Actually this average figure should be $6·95, since " only " 42%, or 75·6 million people, take vitamins. They take them 113 days out of every 365.

**Toilet goods convention**

The Toilet Goods Association, at its 26th annual convention in New York, announced that the industry's 1960 retail sales reached $1·8 billion. A fund was established to conduct on an industry-wide basis the costly testing programme necessary to provide the FDA with the required data in connection with certification of coal-tar colours.

The industry increased its 1960 sales by 7¼%. It reached the $1 billion mark in 1952, and hopes to attain the $2 billion mark in 1961.

Figures for 1960 show that 26·2% of retail sales were made through drug stores; 22·9% through food stores; 20·9% by house-to-house sales; department and speciality stores sold 7·5%, and 8·8% were sold through variety stores.

Mrs. Charlotte Montgomery, columnist for *Good Housekeeping*, emphasised that women want more truthful and helpful information on labels and in advertising. They like unbreakable plastic containers, enjoy using aerosols, but complain when they cannot see how much product is left in them. They want company name and complete address on the label. Women, she said, are concerned about the danger of some products, and should be kept fully informed on this score.

A. H. Lawrence, Jr., of DuPont's Freon Division, said hair sprays, shaving foam and fragrances now account for 40% of all pressurised products and 90% of all pressurised cosmetics. However, sales of aerosol dental creams have dropped substantially, due to difficulty in getting a complete discharge of contents. Deodorants, hand lotions and sham-

poos are the main other products dispensed in aerosol form. Dry sprays and sprays of small particle-size are desirable. The future for aerosol packaging of toiletries is bright.

A number of interesting lectures were given.

J. A. Rogers, Jr., and Z. E. Toth, of Fritsche Bros., reported on the " Instrumental Evaluation of Commercial Citronellols and Geraniols and Their Esters." Their chromatograms showed the various other components which accompany geraniol and citronellol, such as elemene and cadmene.

F. Homburger et al. recommended " The Use of Hairless Mice for Study of Cosmetics." Obviously, the use of human subjects for research is impracticable. Hairless mice respond like humans to substances which smooth and rehydrate the skin. The skin of these mice—which are designated HRBio—develops hair in early life but soon becomes hairless. After 6 to 10 weeks of age wrinkles develop and these increase progressively up to 2 years, due to the accumulation of fats in the skin.

G. R. Clark, of the FDA, speaking on " Some Technical Problems in the Colour Additives Field," noted that many colours will have to be re-investigated; in the toilet goods industry this concerns chiefly the lipstick dyes, particularly the halogenated fluoresceins (the most important of these being D&C Red 21 and D&C Orange 5). But there are several other colours which may require study, *e.g.* D&C Brown No. 1, which is a resorcinol coupling; D&C Black No. 1 which also has several additional components, none of which is black; and D&C Red No. 18, which is a diazo dye. The gist of the problem boils down to a standardisation of specifications.

Dr. P. Flesch, of the University of Pennsylvania, reporting on " *In vitro* Studies on Water Diffusion and Uptake of Human Skin," presented a method to evaluate the " moisturising " properties of cosmetic preparations. He established that callus took up from 60 to 65% water, keratin from 20 to 25%, and the hygroscopic component from 40 to 45% of its weight. In pathologic conditions the uptake ability is reduced.

H. Goldschmiedt, of the Institute of Applied Biology, New York, and I. Lubowe reported on " The Skin Respiration Factor: Evaluation of Various U.S.P. Ointments." They described the oxygen consumption by tissues. This " index of skin respiration " is recorded in millilitres of oxygen per milligram of wet skin per hour. Among the ointments which were found to stimulate were the following: hydrophilic, rosewater, bacitracin, neomycin, and blue ointments. Chrysarobin ointment and sulphur ointment were found to decrease the factor as did ammoniated mercury and the yellow and white waxes.

### Folic acid can be dangerous

Folic acid is known to mask the symptoms of pernicious anaemia when added in sufficient quantities to the diets of persons with this disease, thus interfering with early diagnosis and treatment. For this reason the Food and Drug Administration (FDA) now forbids the sale of vitamin preparations containing more than 0·4 mg. folic acid per daily dose, except on prescription.

### Disease-free cattle for new lab

Important for veterinary and human drug and medical research is the new National Animal Disease Laboratory at Ames, Iowa. A herd of 117 breeding cattle, which has been maintained free of disease for more than 20 years, has been shipped from the U.S. Agricultural Research Center at Beltsville to the new laboratory to provide healthy animals for research. Eventually these animals will be used to breed disease-free animals for disease studies.

The new laboratory possesses also 2,500 guinea pigs, 500 chickens, 60 rabbits, and a breeding herd of 25 hogs. These animals are from groups maintained at Beltsville for many years to supply research subjects of known pedigree and health for disease research. All animals were transported in air-conditioned, temperature-controlled cars and accompanied by veterinarians to ensure their health and safety.

This $16 million laboratory is located on a 318-acre tract of land and consists of seven major buildings and 25 field buildings.

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THE TECHNICAL PRESS IN AUGUST

## Fuel Economy in Chemical Factories

**Chemical and Process Engineering** publishes a special feature dealing with fuel economy, consisting of three articles: " Fuel Economy in the Chemical Industry," " Modern Trends in Boiler Design " and " Boiler Heat Transfer." The series on constructional materials for chemical plant continues with a description of the uses of glass. There is also a review of the Achema 1961 Exhibition.

A survey of anticorrosive elastomeric linings for industrial use is published in **Corrosion Technology,** dealing with various types of linings and their properties.

**Petroleum** prints the second article in the series " Leaders in Oil " with an extensive survey of the operations of the Royal Dutch/Shell Group. Another important article investigates the development of petrochemicals in Britain and the present state of the industry. Many facts and figures, hitherto unpublished in this country, are included.

**Fibres and Plastics** reviews surface coatings and impregnating equipment for fabrics. Other articles include: " Reinforced Plastics in Chemical Engineering." " Reinforcements in Premix Mouldings—Effects of Processing Variables " and " Reinforced Plastics at Interplas 1961."

Articles in **Paint Manufacture** deal with flexographic inks, refrigerator finishes and fluorescent paints.

**Automation Progress** discusses the use of spectroscopy in the automation of forging plants. In another article there is a description of a computer employed in controlling a refinery process.

This month's factory visit described in **Food Manufacture** is to the Distillers Co. yeast factory at Dovercourt, Essex. The special feature reviewed this month is filtration in the food industry and deals with equipment and techniques.

**World Crops** reports on the Aberdeen Irrigation Conference. Other articles include " Coffee Pruning " and " The Mechanisation of Small Farms."

**Dairy Engineering** reviews transport and distribution problems in three articles: " Distribution Problems of the City Retailer," " Distribution Problems of the Producer-Retailer " and " How a Board Runs Its Own Transport."

A description of the International Construction Exhibition is published in **Public Works and Muck Shifter.**

*For specimen copies apply to the Circulation Manager, Leonard Hill House, Eden Street, London, N.W.1.*

### ▶VERSATILE STILL

The Dore still is now put to a variety of uses due to its reasonable cost, compactness and reliable performance. For example, it will provide a steady supply of high strength alcohol from mixtures having a specific gravity of 0·967 and will give a distillate of 0·815 s.g. or higher. It is of particular interest to the essential oils chemist, for it can be designed to work under atmospheric pressure or full vacuum and can be made in copper or stainless steel.

This still is not the only one made by John Dore and Co. Ltd., who design and manufacture many types of equipment for batch or continuous working, but it is the one most frequently supplied because of its adaptability for handling batches (25-5,000 gal.) of a large variety of materials from which it is required to recover the volatiles. The method of heating can be supplied to suit the user, such as solid fuel where no other means of heating can be provided, electricity, oil, gas or steam—which is usually the most economical heating medium.

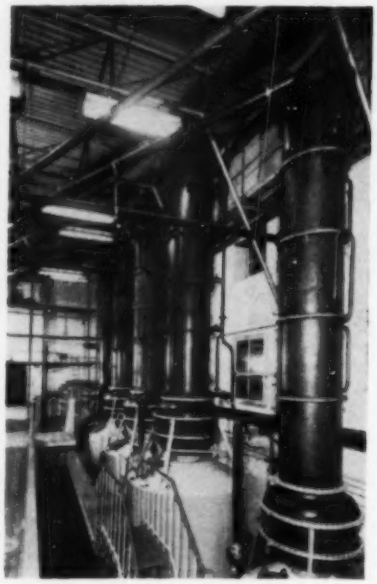
Unlike other stills which can be made and fitted with bubble caps and many other scrubbling devices, this apparatus is unique in that the column contains water jacketed vapour chambers, the number and size of which vary according to the strength of the charge and the specific gravity or purity of the final product.

By using water jackets it is possible to obtain a very wide range of reflux ratios without employing a separate reflux splitting device.

Once the still has been started it requires the minimum of supervision. It occasionally requires attention to the steam and water supply towards the end of the process, unless automatic regulators are incorporated.

### ▶OVENS AND HUMIDITY CABINETS

A laboratory oven with forced air circulation made by Hedin Ltd. is claimed to provide close and reliable temperature control up to 300°C., together with uniform temperature distribution. The control system used gives a maximum temperature differential of $\pm\frac{1}{2}$°C. and



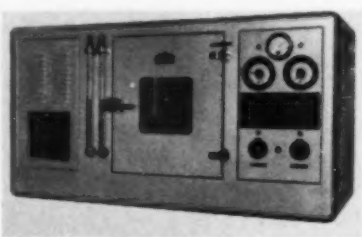
**Dore rectifying stills; a new installation.**

the maximum gradient throughout the working area is $\pm 1$°C. Inside the oven is 16 in. × 16 in. × 16 in. The exterior is finished in an attractive hammer grey and the interior in white epoxy resin.

Another Hedin product is the Type 755/R humidity cabinet. This is constructed in stainless steel and is a Ministry approved unit for the durability testing of plastics and chemicals. Refrigeration is available on all models, and non-standard units can be made to special requirements.

### ▶TEMPERATURE CONTROLLERS

Two additions to their range of mercury-in-steel temperature controllers have been introduced by the British Rototherm Co. Ltd.



**Hedin humidity cabinet Model 755/R with automatic control and refrigeration unit.**

The first, now in production, is a three-stage controller to operate on rise or fall of temperature. It can be set, if necessary, to show a warning light, followed by an alarm bell, and with a complete cut-off of plant at the third stage. It can also be set to give a continuous warning. The controller is available in any range within the limits of −30°F. to +1,200°F.

The second new unit is a temperature recorder-controller which will control between fixed differentials and record the temperatures on a chart. It is now ready for production.

It consists of a chart temperature recorder with the addition of hand-set electrical contacts which operate a self-contained plug-in electronic relay unit for on/off control.

### ▶ANHYDRIC INCUBATORS

Where temperature fluctuations not exceeding 2°C. are unimportant in incubation techniques, anhydric incubators offer attractive savings in cost compared with water-jacketed types. The new B.T.L. anhydric incubators are claimed to have good thermal stability, coupled with exceptional reliability, over a temperature range from 25°C.-110°C.

The large incubator has a polished aluminium chamber, 18 in. high × 16 in. wide × 16 in. deep, fitted with runners so that the three perforated aluminium shelves supplied with each incubator can be used in any three of eight possible positions. An inner door of toughened plate glass with a spring catch protects the chamber. A tubulure in the top of the incubator allows a thermometer to be inserted into the chamber. Temperature is controlled by a B.T.L. bi-metallic regulator, the operation of the regulator being indicated by a pilot lamp. Temperature setting is simple, and unauthorised or accidental interference with the setting is precluded by a locking device. Internal temperature variation at 37°C. is less than 1°C. over long periods, irrespective of large ambient temperature changes. Identical cultures, chosen for their intractability, when incubated in this incubator did not differ from batches held in a water-jacketed incubator for the same period.

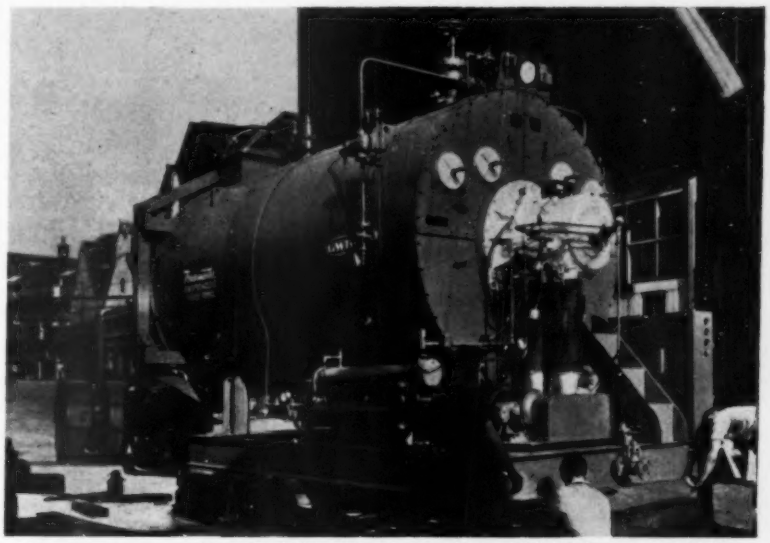
This incubator, finished externally

in ivory stoved enamel, has an overall size of 32½ in. high × 24 in. wide × 24¼ in. deep. It is supplied with 6 ft. of three-cored mains lead, has a consumption of slightly over 100 W at 56°C., and can be supplied for operation on 100-110 V., 115 V., 120-130 V., 200-210 V., 220-230 V., or 240-250 V., a.c./d.c.

The smaller B.T.L. anhydric incubator, of similar construction, has a chamber 12 in. high × 10 in. wide × 10 in. deep and is supplied with two shelves which can be used in any two of five possible positions. It has an overall size of 24¼ in. high × 16¾ in. wide × 17 in. deep and can be supplied for operation on 100-125 V., or 200-250 V., a.c./d.c. The large model costs £69 10s. and the small one £47 10s.

### ▶PACKAGED AUTOMATIC BOILER

With a guaranteed thermal efficiency of 83% the model 400 Powermaster packaged boiler is capable of raising 13,800 lb./steam per hr. (F. &. A. 212°F.). Manufactured by G.W.B. Furnaces Ltd., the oil-fired Powermaster is 19 ft. 3 in. long, 9 ft. wide and 13½ ft. high and weighs about 40,700 lb.

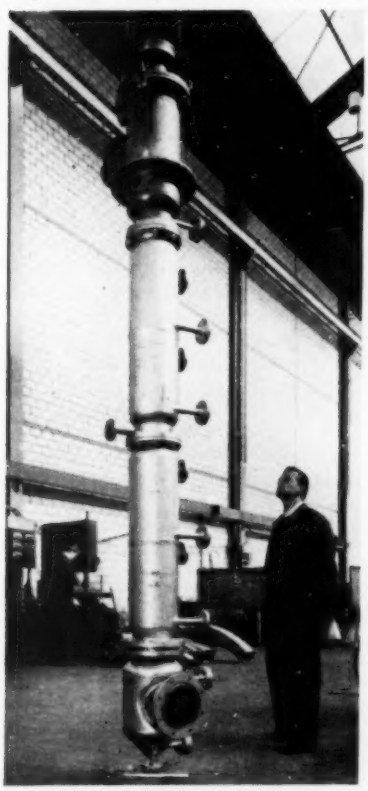


**Powermaster packaged oil-fired boiler made by G.W.B. Furnaces Ltd.**

G.W.B.'s 1,000th Powermaster is shown in the photograph.

The Powermaster incorporates the *Voriflow* medium air pressure burner. Other features include automatic and safety controls fitted as standard on every unit, rapid start up, smokeless operation, single installation and easy maintenance.

The range now comprises 17 models with outputs of from 517 to 24,000 lb./hr. Each unit can be arranged to deliver steam up to 250 p.s.i. pressure; or supplied as low, medium or high pressure hot water boilers, either flooded or with steam space. Suitable oil fuels range from diesel oil up to 3,500 secs. Redwood No. 1 in all but the smallest sizes; or town's gas may be used. Alternatively, an oil/gas combination can be burned.



**New fractionator made by Luwa (U.K.) Ltd.**

### ▶FRACTIONATOR FOR HEAT-SENSITIVE SUBSTANCES

A new fractionator has been developed for the efficient separation of mixtures of high-boiling and heat-sensitive substances. In conventional columns such substances are exposed to the harmful effect of high temperatures at pressures above 20 mm. absolute and cannot be fractionated satisfactorily, if at all.

The manufacturers claim that the new apparatus permits the sharp separation of multi-component mixtures at pressures of about 1 mm. absolute and with minimum pressure drop, a large number of equivalent theoretical plates, high throughput and the shortest hold-up time. The completely new principle depends on alternate evaporation and condensation in a thin film and the device operates continuously as a stripping or fractionating column or in combination. A thin layer evaporator is used as reboiler.

The equipment is supplied by Luwa (U.K.) Ltd., London.

### ▶SEPARATOR FOR OIL EFFLUENT

An improved gravity type separator for refinery effluent, designed by Royal Dutch/Shell, gives about 40% reduction in the oil content of the effluent compared with the conventional type of gravity separator.

Parallel plates in the separator act as collecting surfaces for the oil globules in the effluent. The plates are tilted to guide oil to the surface and sludge to the bottom.

Conventional gravity separators are designed to remove all free oil globules larger than 150 $\mu$ in diameter. Smaller globules or globules loaded with heavy solids, may pass out of the separator and under adverse conditions produce a relatively high oil content for the effluent. Parallel plate installations under test have been found to have materially reduced the oil content of the effluent water.

In one refinery, for example, conventional separators have removed 84% of the oil globules in the range of 120-150 $\mu$, plus an appreciable amount of the smaller sizes. The parallel plate separator, on the other hand, is removing all globules larger than 90 $\mu$, 93% of the globules between 60 and 90 $\mu$, and 80% of the globules in the 30 to 60 $\mu$ range.

## THE CHEMICAL MARKET

### This month's changes

LONDON.—There are several price changes this month, mostly in fine chemicals.

Increased prices include: **Barbituric acid** up by 10s. to 55s. kg.; **Arsenic trioxide** up by 30s. to £38 10s. ton. **Agar Agar No. 1,** Kobe strip, up 1s. 6d. to 18s. lb. and powder up 2s. to 22s. lb. **Palm kernel oil** up by £3 to £111 ton; **palm oil** up by £1 to £103 ton. **Silver nitrate** up by ½d. to 5s. 3d. in 500 g. quantities.

Reductions in price this month include: **Nicotinamide,** which is down by 6s. to £2 4s. kg., and **nicotinic acid,** down by 2s. 3d. to £1 10s. 6d. **Mercurous chloride** is down by 1s. 3d. to 52s. 3d. kg. **Zinc oxide B.P.** is down by £2 10s. to £103 10s. ton. **Ascorbic acid** is down by 1s. to £2 17s. 6d. kg. **Tartaric acid** is down 8s. to £14 12s. ton in 1 ton lots. **Citric acid B.P.,** powder or granulated, 1-4 cwt. lots in bags, has dropped 14s. to 179s. cwt. **Lysine hydrochloride** 100 g. is down 5s. to 18s. for this quantity, and **aluminium lithium hydride** has dropped 20s. to 100s. per 100 g.

## *Correspondence*

### Wrong source

To The Editor

Dear Sir, Perhaps you will allow me to draw your attention to what seems to be an error on page 149 of the April issue of the Manufacturing Chemist. You mention that Dr. James Taylor "pointed out in his Cantor lectures, for purely geometrical reasons large plants are more economical to operate than small ones; the capital cost per unit of output falls to a quarter for a tenfold increase in capacity." I think it was in my article* that these observations were made.

C. J. Thomas

*Department of Economics*
*The University, Southampton.*

* Published in the *Journal of the Royal Institute of Chemistry,* January 1961. See Manufacturing Chemist, April 1961, page 162.


THE SEPTEMBER ISSUE

Here are some of the articles you can read in next month's "Manufacturing Chemist"

COMPOUNDING PERFUMES FOR THE UNILEVER EMPIRE

SYNTHETIC STEROIDS

DUST AND FUME CONTROL

SMALL-SCALE FILTRATION EQUIPMENT


## FERMENTATION TECHNOLOGY ADVANCES

(*Continued from page* 357)

tent. Interruptions to the conditions during transfer from one fermenter to another must be kept to a minimum, otherwise characteristics of the seed culture may be changed and subsequent product fermentations adversely affected. The aseptic transfer technique must allow for very rapid measurement of an aliquot and its transfer by sterile air pressure to the product fermenter where its agitation-aeration environment can be restored.

This is accomplished by interconnecting all the bottom run-off branches on the fermenters by stainless steel piping of 2 in. bore (Fig. 3). An inoculum measure vessel is connected to this interconnecting line. This unit is a cylindrical, stainless steel vessel, having a vertical, flat, sight-glass. The base of the vessel is flanged and bolted to a flat plate. A sight glass and light are fitted to the top of the vessel which also carries branches for sterile compressed air, an air vent and drain valve for steam condensate. The interconnecting lines and inoculum measure vessel are sterilised with steam and allowed to cool under a positive pressure of sterile air. To transfer portions of seed culture, the fermenter pressure is raised, the pressure in the measure vessel reduced, and the bottom run-off on the seed fermenter is opened. When the appropriate volume has run into the measure vessel, the seed fermenter is isolated and the measure vessel put under sterile air pressure. The bottom run-off valve on the product fermenter is opened and the portion of seed culture is blown in rapidly. The whole operation takes only about one minute and has worked very satisfactorily with a number of mould cultures.

*Sampling system.* The arrangement described in the earlier publication has been modified for pilot plant use to conserve the culture by reducing the amount run to waste each time a sample is taken.

*Addition of nutrients during fermentations.* Sterile nutrient solution is stored in vessels connected to each fermenter. For manual addition, a calibrated 1 litre sight-glass is fitted to the line to the fermenter and portions are added at suitable intervals. Alternatively a peristaltic pump can be employed and the rate of flow varied by using tubing of different internal bore.

### Oxygen transfer in fermenters

The technique described by Cooper, Fernstrom and Miller for measuring the rate of oxidation of sodium sulphite solutions has been widely used for comparing the rates of oxygen transfer effected by the agitation-aeration systems installed in aerobic fermenters. Such measurements are only a rough guide because physical conditions in a culture differ considerably from those in an aqueous solution of sodium sulphite. Various factors arise, *e.g.* foaming, which impose limits to the production of consistent fermentations in laboratory fermenters. In pilot plant fermenters foaming out and mycelium deposition are not such a severe problem and a wider range of conditions can be employed for fermentations on this scale.

### Conclusion

The experience that has been gained in operating laboratory and pilot plant fermenters has aided the investigation of batch processes, such as penicillin, of up to 8 days' duration where maintenance of pure culture has not produced any particular problems. A limited number of tests have been run for 21 days with success. Since the laboratory fermenters were designed to run without supervision outside the normal working day, a result is that more antifoam per unit volume has been employed than with pilot plant fermenters. It seems most practicable to site the laboratory fermenters and pilot plant fermenters all in the same area so that shift operators can give the same degree of supervision to both at times when staff supervision is not available.

## THERAPEUTICS

(*Continued from page* 370)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17. E. Shanbron *et al.*, *ibid.*, 1960, **174,** 1702.
18. D. M. Bergenstal *et al.*, *Ann. int. Med.*, 1960, **53,** 672.
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27. R. Dofek *et al.*, *J. Pharm. Sci.*, 1961, **50,** 161.

# Cutting Down the Drug Bill

MEASURES which have been taken to control the size of the N.H.S. drug bill—now costing £100 million a year in England and Wales alone—were discussed in a Commons debate last month (July).

Mr. Enoch Powell, Minister of Health, said that reductions in price which had been made following introduction of the improved Voluntary Price Regulation Scheme had been worth £1,750,000 in a full year. It was a useful beginning but only a beginning. Referring to the decision to use the Patents Act for the purchase of certain widely used drugs by the hospital service, the Minister said that new contracts covering these drugs would be in force by September 1. He could not estimate the saving since final prices were not fixed, and there would also have to be negotiations over royalty payments.

Mr. Powell said that the recommendation of the Cohen Committee on prescribing, published last March, eliminated no effective drug from the armament of the general practitioner. Nevertheless, it could result in true economy in prescribing. The new bi-monthly *Prescribers Journal*, he believed, would find a place among the means on which the general practitioners relied for assistance in their prescribing work.

Speaking of the cost of drugs in hospitals, Mr. Powell said that regional boards had been active in drawing the attention of hospitals to " apparently unexplained excesses." In a number of cases this had resulted in real improvements in the economy of hospital prescribing.

The Health Minister told M.P.s that he had asked the Standing Committee on Operational Research in the Pharmaceutical Services to advise him about research into prescribing patterns, with particular reference to habit-forming drugs such as the amphetamines and phemetrazine. Research in this field had been suggested by the Brain Committee on Drug Addiction.

Mr. Kenneth Robinson (Labour, St. Pancras, N.) said these drugs now comprised about 2½% of prescriptions. They were addiction-forming and might lead to serious psychosis. There was a view that the Brain Committee took a rather too complacent attitude about the dangers of drug addiction in this country, remarked the M.P., asking the Minister to keep a close watch on the situation.

### Iron tablets " profiteering "

The suggestion that there was " profiteering " involved in the sale of ferrous sulphate tablets was made by Mr. Laurence Pavitt (Labour, Willesden, W.). After being informed by Miss Edith Pitt, Parliamentary Secretary, Ministry of Health, that at some ante-natal clinics the use of these tablets had been, or was being, discontinued, the M.P. said that one of the most frequent prescriptions which was dispensed was for 84 of these tablets—a prophylaxis against anæmia. " Is she aware that 1,000 tablets cost 2s. and that by retailing 84 for 2s. a sum of 22s. is made on every 2s.-worth sold?" he declared. " Is that not profiteering?" Miss Pitt replied that he had been misinformed because 100 tablets would retail at 1s. 9½d. Though hospitals could do no other than make the standard charge of 2s. there was no reason why doctors should not advise patients to obtain the tablets privately. When Mr. Pavitt said that hospitals purchased these tablets in cartons of 1,000 for 2s. the Parliamentary Secretary pointed out: " That is not the retail price."

### Prescriptions on credit

Owing to the increase in prescription charges, chemists were now having to dispense medicine on credit in cases of emergency, asserted Mrs. Barbara Castle (Labour, Blackburn). She asked the Minister to abolish the charges. Mr. Powell said no.

### Cancer research

Work at the Chester Beatty Research Institute had shown that the incidence of certain types of cancer in mice could be reduced by restricting the number of calories in the diet and that the experimental induction of cancer to the liver in rats could to a certain extent be prevented by supplementing the diet with protein and riboflavin, stated Mr. Denzil Freeth, Parliamentary Secretary for Science.

### Sundrop and Sundrops

Mr. Maudling, President of the Board of Trade, said he would look into a case in which it was reported that a soft drink was being marketed under a name similar to that of a detergent. Mr. Donald Wade (Liberal, Huddersfield, W.) suggested that a detergent known as *Sundrops* could very easily be mistaken by a child for a soft drink known as *Sundrop*, especially as both were sold in the same type of bottle.

## BEECHAM'S THIRD NEW PENICILLIN

Beecham Research Laboratories Ltd., have developed another synthetic penicillin called *Penbritin*. It is claimed to be active against more strains of bacteria than any previous penicillin. It is stable in the presence of acid and not destroyed in the stomach. Being well absorbed when taken by the mouth, it is prepared in oral capsule form.

This new drug has its origins in the discovery by Beecham scientists in 1957 of the existence of the penicillin nucleus (6-amino-penicillanic acid) and the method of isolating it.

In October 1959, *Broxil*, a powerful oral penicillin was marketed by Beecham. For the first time it became possible by oral administration to produce concentrations of penicillin in the blood higher than those following injections.

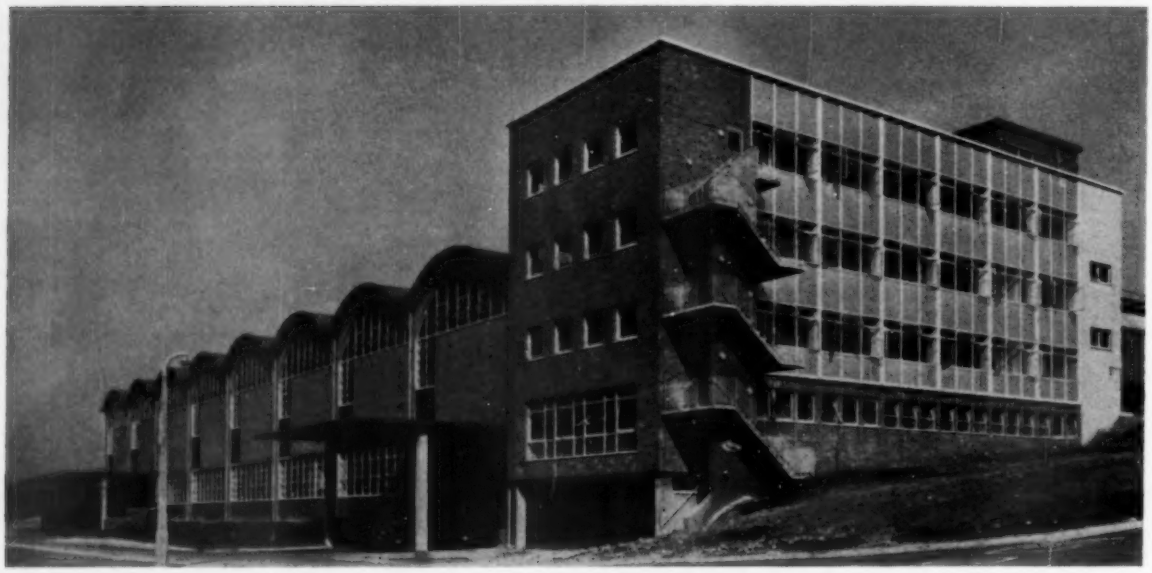
In September 1960 Beecham announced *Celbenin*. This synthetic penicillin is effective against the hitherto resistant strains of *staphylococci*, which were a particularly grave problem in hospitals.

The latest product is the third major objective to be reached in the development of synthetic penicillins. Among the hundreds of new synthetic penicillins made in the Beecham laboratories at Brockham one, with the chemical formula 6[D(-)α-aminophenylacetamido] penicillanic acid, now known as *Penbritin*, was found to be highly interesting. It is active against certain bacteria unaffected by other penicillins and, against some strains, is more active than any other antibiotic in general use.

The new discovery means that a penicillin now exists capable of dealing not only with organisms normally sensitive to penicillin but also with those associated with urinary tract infections and chronic bronchitis. As indicated in the *B.M.J.* (July 22), laboratory tests of *Penbritin* also show high activity against typhoid fever and food poisoning bacteria.

# *How Wellcome Handle a Thousand*

★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★★



**Wellcome's new £100,000 warehouse and office building at Dartford, Kent. The concrete barrel vault roof needs no internal supporting pillars, thus giving unobstructed floor space. The sloping site gives road access to both floors.**

EVERY 30 seconds of every working day an order is dispatched from the Wellcome Foundation Ltd. at Dartford, Kent. This comes to 5,000 orders a week, about a third of which go abroad. A single order may consist of two bottles or two crates weighing several hundred pounds. The customers are retail chemists, hospitals, farmers and wholesalers. All want to be served quickly, so the aim is to deal with every order on the day it is received. Many orders are of a "life and death" nature; these can be on the way to the customer within ten minutes of receipt.

The system capable of meeting these exacting requirements must be flexible, smooth running and, above all, accurate. It must receive, check and store in the right conditions all goods sold by Wellcome. Biologicals have to be stored at low temperature. Narcotics have to be stored and handled in a locked compound. All goods are subject to a rigid "first-in first-out" control to make sure none are kept too long before dispatch.

These demands are now being met in a new warehouse at Dartford. It consists of a sub-basement and a main floor, each 240 ft. long by 100 ft. Total floor area is 48,000 sq. ft. and this includes a 45,000 cu. ft. cold store and a narcotics compound. At one end of the building is an office block, 100 ft. long by 30 ft., comprising a sub-basement garage, a basement with canteen and lavatories, and three office floors.

The warehouse was designed by work study. First a model was made and with its use the best disposition of storage and packaging areas and equipment was decided on. The building is of reinforced concrete and the most impressive feature is the concrete barrel vault roof. It requires no pillars for support and enables the whole of the main floor to be a single unobstructed area which makes for maximum flexibility. Particular care has been taken not to clutter walls or floor with piping or other obstructions.

Conveyor belts run the length of one side of the main floor. Orders are assembled from stock shelves immediately behind the packers. They are placed in trays and conveyed to the checkers. They are then sent to the packers via a central depot where the correct size of carton is placed with each order. Orders which include narcotics are tracked downstairs to the Dangerous Drugs compound, where they are handled under Home Office regulations.

Goods stored on pallets are handled by fork-lift trucks and a lift big enough for these trucks connects both floors.

A thousand parcels a day are dispatched by parcel post. Each contains on average at least three different products in varying quantities. An average of 35 dispatches a day are sent by passenger trains at hourly intervals through London main line stations. About 30 orders a day are sent to wholesalers in the London area by van.

About 1,150 crates and parcels a week are sent overseas.

Urgent orders short-circuit the system and can be dispatched in 10-15 min. At weekends emergency arrangements enable S.O.S. orders to be filled. The new warehouse is a great improvement on the old system of handling orders from a number of different buildings pressed into service as the business grew. Labour requirements have been reduced by

## *Orders a Day*

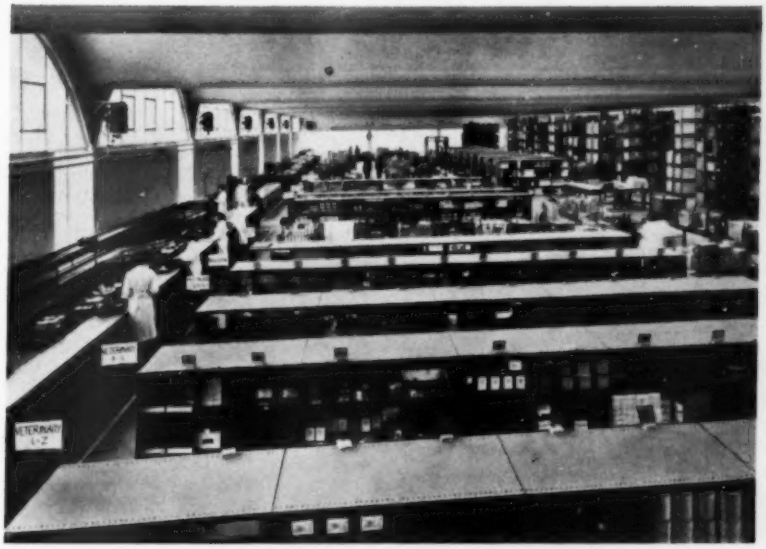
★★★★★★★★★★★★★★★

20%, stock control is more efficient, and now *all* orders can be dealt with the same day they are received.

Wellcome have spent £100,000 on the new warehouse, which can comfortably handle 50% more work as the business grows.

**CONTRACTORS**

Main contractor
John Mowlem and Co. Ltd.
Heating
G. N. Haden and Son. Ltd.
Granolithic
Johnson Floor Co. Ltd.
Scaffolding
Scaffolding (Great Britain) Ltd.
Floor tiling
Semtex Ltd.
Partitions
Sankey Sheldon Ltd.
Sewage disposal
Wallwin (Pumps) Ltd.
Conveyors
British Wedge Wire Co. Ltd.
Fork-lift trucks
Lansing Bagnall Ltd.



**In this photo most of the 24,000 sq. ft. of unobstructed floor space on the first floor can be seen. The concrete barrel vault roof is unplastered but painted a light cheerful colour. Natural light enters through roof windows. Orders are processed on the conveyor belt, moving steadily through at the rate of a thousand a day.**

**The 45,000 cu. ft. cold store for the storage of biologicals and other sensitive products. Rigid temperature control prevents freeze up. The pallets on which the goods are stored are handled by fork-lift truck which is transported to top floor in special lift.**

**Dechema**. The Deutsche Gesellschaft für chemisches Apparatewesen has published a 16 pp. brochure which gives information on the aims and tasks of the Dechema. This publication in English, French and German is available free from Dechema, Frankfurt am Main 7, Postfach 7746.

**Liquid mixers.** Premier Colloid Mills Ltd. have issued three new specification leaflets for all portable and side-entry mixers. There is a separate leaflet describing the action and properties of the Dispersator mixing head. Premier Mixers include portable and semi-portable units up to 2½ h.p., top entry (fixed) units up to 5 h.p., side entry mixers up to 12½ h.p., and the complete range covers speeds of 30, 60, 400, 1,500 and 3,000 rpm. and quantities from 1 gal. to 100,000 gal.

**Industrial chemicals.** Robinson Brothers Ltd. have produced a catalogue of their chemicals for industry. They range from dithiocarbamates and thiuram sulphides to amines and thioacids and derivatives.

**Molten sulphur.** Advice on the handling and storage of molten sulphur is given in a booklet published by F. W. Berk and Co. Ltd. The company now distribute most of the molten sulphur output of the U.K. refineries of British Petroleum, Esso and Shell. By taking delivery of sulphur in a molten state, the user secures a purer uncontaminated product, free of dust, capable of being handled automatically by pumps, and requiring less storage space. His fire risk and corrosion losses are reduced and he will require less heat to keep the molten sulphur ready for use than he would to melt a comparable quantity of powdered sulphur. Copies of the booklet "Molten Sulphur" are available from F. W. Berk and Co. Ltd., Stratford, London, E.15.

**Exhibition pre-view.** Here is another selection of exhibits to be shown at the Packaging Exhibition, Olympia, September 5-15.

### Tape dispensing and cold-seal paper

*Samuel Jones and Co. Ltd.*, will be showing hand-operated and electric *Tapeshooter* machines for dispensing, measuring and moistening and cutting their *Gumstrip* and *Balestrip* sealing tapes at high speed. Two hand-operated models are available for accommodating tape up to 4 in. (10·1 cm.) and up to 8 in. (20·2 cm.) wide in lengths between 4 in. (10·1 cm.) and 36 in. (91·4 cm.). The length is pre-set on a drum scale. The electric model handles tape with widths up to 4 in. (10·1 cm.) and lengths up to 50 in. (127 cm.) at a speed of 2 ft. (60·7 cm.) per sec.

A heating element is incorporated in the 8 in. (20·32 cm.) and electric *Tapeshooters* to ensure instant adhesion in cold weather.

A range of cohesive coated papers will also be displayed, which seal by pressure only and provide resistance to moisture, moisture vapour, fat and corrosion. They were developed in Sweden by Billingsfors under the trade name *Cosil*.

### Printing machines

*Rejafix Ltd.* will be showing a new fully automatic machine for printing cylindrical articles in all types of material at speeds between 3,000 and 7,000 per hr. A special feature is the bowl-feed attachment from which articles, which may be loaded indiscriminately, are automatically extracted and fed to the printing unit in the correct position. Printing area is $3 \times 2\frac{1}{4}$ in. ($7{\cdot}62 \times 5{\cdot}72$ cm.).

Another new machine will be the air-operated Devon 20 for the offset printing of irregularly shaped objects over a printing area of $4\frac{3}{4} \times 3$ in. ($12 \times 7{\cdot}62$ cm.). A new automatic tin over-printer, the E1/T Mark II, will also be shown for the first time.

### Imprinting and coding machines

*Mark-O-Print Ltd.* will be showing their new inkless *Wrap-a-Printa* machines which use pigmented roll leaf instead of ink to produce permanent opaque impressions on any packaging material in web form. The machine is designed for attachment to any type of packaging machine, and models with printing areas from $\frac{3}{4}$ in. square (1·9 cm.) to 4 in. square (10·1 cm.) are available.

Another exhibit will be the new *Rolaprinter*, a miniature flexographic printing unit for use in conjunction with automatic packaging machines; it gives a registered imprint of contents, price or code date on cellulose film, waxed paper, Kraft paper, metal foil and plastics.

**Seamless aluminium cans, with the top ridged then curved inward to take the white polythene snap-on cap, contain 100 tablets and 50 tablets of "Anadin." Printed in green and yellow on white, the cans are produced by Venesta Metal Containers Ltd.**

### Weigher-fillers and letter printers

Two fully automatic Italian machines, the DA/1 weigher-filler for high viscosity liquids, and the SA/1 Letter printing machine, for cylindrical containers, will be shown by *Mason and Morton Ltd.* In both models a conveyor supplies the containers, to a gravity hopper unit for the DA/1 where they are precision weighed before filling, and direct to the SA/1 for correct printing. For the DA/1 output speeds vary between 1,200 and 1,600 containers per hr.; and for the SA/1 the speed is 1,800 per hr. Filling tolerances are $\pm 2$ grams %. A lid sealing unit is standard on the DA/1 model.

**The new Grip-a-Tab model HDA hand dispenser is made by P. P. Payne and Sons Ltd. It can be used with all pressure sensitive tapes on 3 in. centre cores from $\frac{1}{4}$ in. to 1 in. wide and up to 8 in. diameter rolls.**

### Dispenser for strapping tape

An improved hand dispenser (Model HDA) is being marketed by *P. P. Payne and Sons Ltd.* It ensures rapid and accurate dispensing, cutting and positioning and it can be carried easily on the job by the packer.

The construction of the dispenser provides a good grip and simplifies the controlled application of pressure-sensitive tapes. A special feature is the easily replaceable cutter blade, which for safety has been designed to cut tough strapping tapes, without being razor sharp. Though it can be used with all pressure sensitive tapes on 3 in. centre cores from $\frac{1}{4}$ in. to 1 in. wide, and up to 8 in. diameter rolls, it is suited to dispense Payne's *Superseal* strapping tape, manufactured from high tenacity rayon threads bonded together to form a weftless tape, backed with a high tack latex adhesive. It is intended for heavy-duty packaging where its high breaking strength can be used to advantage.

### Pneumatic extraction of bottles from cartons

An automatic machine with single, double or triple heads, for extracting bottles from cartons at speeds up to 9,600 per hr., will be exhibited by Dawson Bros. Ltd. Twenty-four cartons per min., containing bottles with capacities between $\frac{1}{4}$ pint (0·189 litre) and 1 quart (1·136 litres) can be delivered on to a drag-bar conveyor which halts them beneath a grab head. In the head, carton sides are squared by a locating frame, which also secures the interior partitions. A set of nylon grippers then descends to grasp the bottles, withdraw them pneumatically and remove them to another conveyor. Air consumption is approximately 0·75 ft³ (0·021 m³) per carton.

### Polythene containers

Metal Box are now making *Rigidex* high-density polythene *Poly-Tainer* bottles in 1 gal. and $\frac{1}{2}$ gal. sizes. They are suitable for many liquids, *e.g.* oil-in-water emulsions, certain polishes, detergents and most water-based products, including acids and alkalis.

To save space in transit they are being made in a modified square shape and their weight is negligible in comparison with the weight of the contents.

The translucent self-coloured polythene allows both the colour and the level of the contents to be seen. Silk screen printing is being offered in one colour, or the containers may be embossed or labelled.

The wide non-drip neck is closed by a two-start compression moulded polystyrene cap with special knurling, fitted with a wad faced with either polythene or *Vinylite*.

## Coal injection, drug research—two themes at S.C.I. meeting

**Lord Fleck (right), president of the Society of Chemical Industry and former chairman of I.C.I., talks to Mr. L. S. Mumford, development controller of I.C.I., at the Society's annual meeting in Oxford.**

THE Society of Chemical Industry held its annual meeting at Oxford, for the first time in its 80 years' existence. Lord Fleck was re-elected president for another year and the principal officers were also re-elected.

At the formal a.g.m. on July 11, the treasurer, Dr. Ferguson, presented a very favourable financial report. For the first time in many years income appreciably exceeded expenditure. Cash at bank and in hand at December 31 amounted to £42,682 against £5,360 the year before.

In his address Lord Fleck referred to the importance of increasing membership and suggested that a small number of free subscriptions to the Society's journal be given to students at the Colleges of Advanced Technology. (See editorial note in this issue.)

**Coal injection.** Lord Robens, chairman of the National Coal Board, was chief guest at the annual dinner held in Keble College. He announced a revolutionary new technique for reducing the cost of iron and steel manufacture. Milled coal, instead of coke, is to be injected into blast furnaces in the N.C.B.'s programme of trials now in hand. At least 30% of the coke used in furnaces could eventually be replaced when the technique has been fully proved, said Lord Robens. Coal is injected automatically into the furnace through lances placed usually in the blast furnace tuyeres, the amount being accurately controlled to suit furnace conditions. The injection equipment was being specially designed by Petrocarb Inc., the U.S. firm which recently pioneered the full-scale application of coal injection in the United States.

**Drug resistance.** The S.C.I. Medal was awarded to Sir Cyril Hinshelwood, past-president of the Royal Society. His address was called "Some observations on the physical chemistry of cell mechanism." Discussing drug resistance, Sir Cyril said: "We have a clear picture of two kinds of drug resistance, one, the negative one, in which the cell is protected by its inability to take up the drug. This kind could easily arise by the destructive action of radiation. In the second kind, a positive kind, the cell actively adapts itself by the development of a new reaction pattern which by-passes or antagonises the action of the drug or develops enzymes capable of destroying it. With two such powerful mechanisms available it would be surprising if nature did not make use of both."

**Drug research.** A paper reviewing problems of drug research was given by Dr. F. L. Rose of I.C.I. He said the industry is accused of being profligate in its research strategy and adjured to rationalise its approach. The development of sulphonamides 20 years ago gave promise of developments in this direction. But the discovery of the 250 synthetic drugs now in the B.P. came about largely by the established methods of analogy research. This was caused by a host of structure/biological effect relationships coming into play. The striking effect of structural changes on the comparatively simple matter of drug absorption and excretion was illustrated by reference to sulphonamide derivatives. An extensive search for a new anti-asthmatic drug based on structures analogous to the purine bronchodilators ended in completely unpredictable failure in the human subject although the laboratory campaign was successful.

### More nitrogen for I.C.I.

A new plant which will increase the production capacity of nitrogen supplies to the Wilton Division of I.C.I. by 50% is to be built by British Oxygen at their Middlesbrough works.

Costing about £500,000 the plant will have a capacity of 5,000 cubic metres per hour of very high purity nitrogen.

### Upjohn expand at Crawley

Upjohn Ltd. have commenced building a £450,000 extension to their pharmaceutical plant at Crawley, Sussex. Plant and equipment installed will cost £250,000. The new building will consist of a new pharmaceutical production area, control laboratories, additional office and storage space.

The factory will supply antibiotics, steroids and anti-cholinergics; they should be in full production by the end of 1962.

### New weights Bill affects drugs, toiletries and aerosols

The changeover to metric units in the pharmaceutical industry will be facilitated by the new Weights and Measures Bill. It is a revision of the original bill and it will probably be considered in the next session of Parliament. Clause 10 (7) provides for a changeover to the use of metric units by pharmacists while leaving doctors free to continue to prescribe in apothecary units.

New safeguards for the consumer incorporated in the bill include the addition of a wide range of pre-packed perfumery and toilet preparations as well as anti-freeze liquid and linseed oil to the commodities which must carry details of quantity or capacity measurement.

The eighth schedule of the bill is wholly new and covers liquid fuel, soap, detergents and paint. "Scheduled" goods sold in aerosol form must state either the quantity, by weight or measure, of the active ingredient or the total weight of this ingredient plus the propellant.

It is expected that the Bill will be discussed by local authorities, traders and industry before being introduced to Parliament.

### Pfizer Sabin vaccine approved

The Ministry of Health has approved the sale of the Sabin live oral poliomyelitis vaccine produced by Pfizer Ltd. at their polio vaccine unit at Sandwich, Kent. The vaccine has undergone rigorous tests carried out by the Medical Research Council. Oral vaccine is not being used except in emergency. Pfizer's vaccine, however, will be available for export.

Sample batches have been submitted to the U.S. public health authorities for licensing.

**Prescriptions cost nearly £80m.**

Chemists dispensed 218,685,118 prescriptions during 1960 at a total cost of £79,193,781 and an average cost per prescription of 7s. 2·92d. The total number of prescriptions was about 4,600,000 more and the total cost over £6 million up on 1959. An increase of 5d. in the average prescription cost was mainly due to the prescribing of more expensive drugs, either those introduced in previous years or those newly marketed. Tablets continue to displace mixtures.

These figures are given in the Report of the Ministry of Health for 1960 in which it is stated that the total actual cost of the National Health Service in England and Wales in 1959/60 rose to £726¼ millions from £671 millions in the preceding year. This increase of 8·2% compared with an increase of approximately 3·4% in the national income between 1958 and 1959.

Since 1956, 42,109,220 doses of polio vaccine have been distributed to local health authorities; of these 22,686,920 were of British-made vaccine and 19,422,320 of vaccine imported from Canada and U.S.A.

**P.T. on antiseptics and disinfectants**

Customs and Excise have reviewed the liability to purchase tax of antiseptics and disinfectants. It has been decided that such a product is within the scope of Group 32 or Group 33 of the tax schedule if it is described as an antiseptic or as a general purpose germicide, or if the label, literature, or any form of advertisement of the product includes references to its suitability for use as an antiseptic, gargle or mouthwash, or for any other toilet or medicinal purpose.

To allow manufacturers of disinfectants time to make any alterations that they wish in their marketing arrangements this decision will not operate until January 1, 1962.

**Codex amendments**

The Pharmaceutical Society has made the following amendments to the British Pharmaceutical Codex 1959:

p. 125 Calcium Hypophosphite
p. 431 Manganese Hypophosphite
p. 602 Potassium Hypophosphite
p. 692 Sodium Hypophosphite
*Phosphite*. Delete this requirement.

**Therapeutic Substances Act additions**

The following substances have come within the scope of the Therapeutic Substances Act, 1956, Part II:

(*a*) amphotericins and any salts of amphotericins,
(*b*) demethylchlortetracycline and any salts thereof,
(*c*) framycetin and any salts of framycetin,
(*d*) kanamycin and any salts of kanamycin,
(*e*) ristocetins and any salts of ristocetins,
(*f*) vancomycin and any salts of vancomycin,
(*g*) esters of erythromycin and any salts of such esters,
(*h*) any substance the chemical and biological properties of which are identical or similar to these substances, but which is produced by other means.

**Cyanamid enter Common Market**

Cyanamid International is to build a second European antibiotics plant at the Catania, Sicily, headquarters of Cyanamid Italia. It will cost a million dollars. It will be the company's first antibiotic fermentation unit within the European Common Market.

Like its British equivalent at Gosport, the Catania plant will produce the main broad spectrum antibiotics, Ledermycin (demethyl chlortetracycline), Achromycin (tetracycline), and Aureomycin (chlortetracycline), as well as various other therapeutic agents. It will also supply Aureomycin animal feed supplements and veterinary products.

**Solvent extraction plant**

Blaw Knox Chemical Engineering Co. Ltd. has been awarded a contract by J. Bibby and Sons Ltd. to furnish a plant for the solvent extraction of soya beans and other oilseeds. The plant, to be constructed at Liverpool, will supersede an existing solvent extraction plant, and the programme, which is scheduled for completion by March 1962, will be arranged to minimise interference with existing production.

**Water scheme for new I.C.I. works**

A major freight operation involving the transporting of 17,000 tons of prestressed concrete pressure pipes from Stanton Ironworks, near Ilkeston, Derbyshire, to the Bristol area is now being carried out by British Railways.

The operation is in connection with the Bristol Waterworks Co.'s Sharpness abstraction scheme which will supply water to the new I.C.I. works at Severnside near Avonmouth and also to the Bristol area domestic water supply.

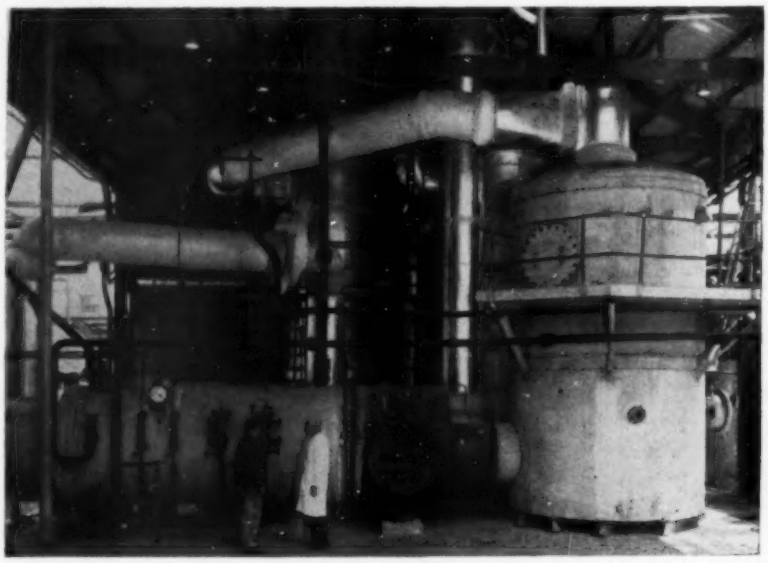
**Balfour build heavy fabrication shop**

On a new 25-acre site adjacent to their research and development centre, Henry Balfour and Co. Ltd. are to build a heavy fabrication shop 300 ft. long by 80 ft. span. The building will be 50 ft. to the eaves and have glass curtain walling on the gables and north side to ensure maximum daylight. The building is designed for two 50-ton E.O.T. cranes. Floor area will be 31,800 sq. ft. The new shop is scheduled to go into production in June 1962.

In addition to this extension, Balfours have recently installed a new 1,000-ton press which is capable of handling dished ends of 10 ft. diameter up to 3 in. thick.

**Company finance**

**Distillers Co. Ltd.** Net profit for 1961 was £17,224,224 (£16,866,424). Total dividend paid on ordinary capital was 13½% (last year, equivalent to 12½%).



**BERK'S NEW ACID PLANT**

*This new contact sulphuric acid plant recently commissioned at Stratford, London, by F. W. Berk and Co. Ltd. will considerably increase production of acid.*

*The plant incorporates a modern fire tube boiler and a four-pass converter. It was designed by Berk engineering staff and Simon Carves.*

**The Geigy Group of companies**

The Geigy Group have elected the following additional directors: The Geigy Co. Ltd.—L. R. Dowsett, A. Hill, T. W. Parton, J. Smethurst; Geigy Pharmaceutical Co. Ltd.—Dr. R. H. Gosling, S. W. Kipling; Ashburton Chemical Works Ltd.—K. M. Townsend B. J. Warr; and James Anderson and Co. (Colours) Ltd.—T. Gibson, K. G. Hargreaves.

Geigy (Holdings) Ltd. have announced that **Viscount Rochdale,** who is a member of their board, will succeed **A. H. Whitaker** as chairman of their subsidiary, James Anderson and Co. (Colours) Ltd. **Dr. F. Buchmeier** has been appointed deputy chairman of that company.

Thomas Hedley and Co. Ltd. have appointed **Dr. J. F. Goodman** head of the basic research department. The department forms part of the Research division at Newcastle upon Tyne.

**Sydney Barratt,** chairman of Albright and Wilson Ltd., received a knighthood in the Birthday Honours. He joined the company in 1932 as assistant director of research, became managing director in 1955 and chairman in 1958.

**A. V. Billinghame** and **P. J. March** have been appointed directors of Shell Chemical Co. Ltd. Mr. Billinghame joined Shell in 1942, and was closely associated with Shell's entry to the chemical business in the U.K. and its subsequent development. He will continue as Regional Co-ordinator III (U.K., Central and South America) with Shell International Chemical Co. Mr. March joined the chemical industry administration of Shell Petroleum in 1949. Last year he was appointed general manager of the newly formed industrial chemicals division.

**W. Morgan Thompson** has been appointed chairman of Miles Laboratories Ltd., British subsidiary of Miles Laboratories Inc., in succession to **Don S. Momand,** who remains a director. Mr. Thompson, who is managing director, becomes the first British chairman. He was formerly a director of Monsanto Chemicals Ltd. He is a member of the Pharmaceutical Society and of the executive committee of the Proprietary Association of Great Britain and also of the public relations committee of the A.B.P.I.

**Dr. G. C. Gibbons,** chief chemist of Domestos Ltd., Newcastle upon Tyne, since 1957, has been appointed technical director of the company. **G. Duncalf,** has been appointed chief chemist in his place. He previously worked for Goddards of Leicester.

**Sir Sydney Barratt**

**W. M. Thompson.**

**J. F. Goodman**

Whiffen and Sons Ltd., a member of the Fisons Group, have announced the following changes in the board of directors: **A. Robinson,** formerly chairman and managing director, becomes chairman; **A. H. Pashley,** formerly director and commercial general manager, becomes vice-chairman; **A. P. Lowes,** formerly director and technical general manager, becomes joint managing director; **A. S. Woodhams,** formerly of Fisons Ltd., becomes joint managing director.

**Analysts' officers**

The Association of Public Analysts has elected the following officers:

*President:* J. H. Hamence,
*Vice-President:* D. D. Moir,
*Hon. Treasurer:* R. C. Spalding,
*Hon. Secretary:* F. A. Lyne,
*Hon. Editor:* E. C. Wood.

The Fullers' Earth Union Ltd., a member of the Laporte Group, has appointed **Dr. A. R. Pinnington** sales manager (development).

Following his retirement from executive duties with the Distillers Co. Ltd., **William Reid** has been appointed chairman of United Glass Ltd. in succession to **L. A. Elgood.** Mr. Reid has been a director of United Glass for 24 years, as well as chairman of its closure-making subsidiary, Kork-N-Seal Ltd., since 1955. Mr. Reid has travelled all over the world to promote the sale of Scotch whisky.

**Thomas J. Milligan,** assistant sales director of Du Pont's electrochemicals department, has been appointed managing director of Du Pont de Nemours International S.A. He succeeds **William D. Eaton,** who has been promoted to assistant European director of the Du Pont Company's international department.

**F. G. Paddle,** until recently head of the industrial sales division at May and Baker Ltd., has been appointed an assistant director of sales. He will handle home and export sales of industrial, laboratory and aromatic chemicals.

**Dr. F. A. Robinson,** at present research director of Allen and Hanburys Ltd., has been appointed executive chairman of the Crookes Laboratories Ltd. Dr. Robinson, who is hon. treasurer and former chairman of the Biochemical Society, and a vice-president of the Institute of Chemistry, will be taking up his duties in September.

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**MC editor to visit U.S.A.**

Mr. W. G. Norris, Editor of MANUFACTURING CHEMIST and Editorial Director of the Leonard Hill Group of publications, will visit New York and Washington October 2 to 20. He will discuss current trends in the pharmaceutical and chemical industries with leading American businessmen and experts.

Mr. Norris looks forward to meeting readers and advertisers of MANUFACTURING CHEMIST and other Leonard Hill magazines and invites correspondence to this end. His address is 9 Eden Street, London, N.W.1.

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**Miss Pears 1961**

The winner of D. and W. Gibbs' annual competition to find the prettiest little girl in the United Kingdom was presented with a £500 cheque by Lady Barnett at a luncheon in the Carlton Tower Hotel, London. Julie Williams of Newport Pagnell, Bucks., "Miss Pears 1961," was chosen from 64,000 contestants and her picture will advertise Pears soap for the next 12 months.

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**Changes of address**

The offices, works and laboratories of Moritz Chemical Engineering Co. Ltd. are now at Thames Side, Kingston upon Thames, Surrey.

Rhodes, Brydon and Youatt Ltd. have moved their London offices to 45/51 Leman Street, London, E.1. Telephone: Royal 1212.

Unicam Instruments Ltd., member of the Pye Group, have moved to York Street, Cambridge.

### Du Pont to make isocyanates in N. Ireland

The second chemical plant to be erected by the Du Pont Co. (U.K.) Ltd., at Maydown, Northern Ireland, will produce isocyanates. These materials are used to make rigid and flexible urethane foams. Rigid foams are used for insulating panels, building panels and other structural purposes. Flexible foams are used for cushioning and for interlining clothing. Other uses are being developed. The foams are made by reacting toluene di-isocyanate with a resin in the presence of a catalyst. Foaming is caused by injecting Freon gas or by inducing $CO_2$ bubble formation in the mix.

The plant will cost several million pounds sterling and will be in operation in late 1963, when it will employ 125 people. The chief raw material, toluene, will be bought from U.K. sources, if possible. Other raw materials will also be bought in the U.K.

Du Pont in the U.S. have been selling isocyanates since 1944. A large plant for making *Hylene* isocyanates was opened in the U.S. in 1956.

In Britain the only manufacturer of isocyanates at present is I.C.I. Isocyanates are cheaper in the U.K. (4s. 8d.-4s. 10d. per lb.) than in the U.S. where they cost about 75 cents per lb.

Du Pont will supply isocyanates; they will not make foams. Their existing plant at Maydown produces neoprene.

### Ciba aids FAO's fight against animal diseases

The full toll of livestock disease in loss of production and wasted labour and feed, says Dr. W. Ross Cockrill, Chief of FAO's Section of Veterinary Medicine, runs into billions of dollars each year.

Recently, the Organisation and Ciba Ltd. reached agreement on joint action against animal disease under FAO's Freedom from Hunger Campaign.

Ciba will contribute the full costs of an expert's field survey in Latin America, it will supply free of charge all amounts of any CIBA products needed by FAO experts in their field work against animal diseases, it will also donate required amounts of these products to governments for field trials when recommended by FAO experts, and finally, the company has offered to finance the preparation by FAO of an urgently needed publication on distomatosis, or fluke disease, which attacks sheep, cattle and goats and affects more than half the sheep-producing countries of the world.

**Emergency meeting.** International action to be taken to prevent the disastrous spread of " emerging " diseases of animals, now threatening the world's livestock industry on a disquieting scale, was discussed at a joint meeting convened in Ankara, Turkey, June 19-28, by the FAO and the International Organisation of Epizootics. Some 40 countries were represented.

Spectacular outbreaks of African horse sickness, blue-tongue, listeriosis, enterotoxæmia, lumpy skin disease, Johne's disease and African swine fever, have focused world attention on the danger of a sudden break-out by such diseases from their " home " areas into countries and regions where they have never struck before. Horse sickness, for instance had always been considered " a typical African disease," but in 1959 it invaded Afghanistan and West Pakistan, and has since spread rapidly to Iran, Iraq, Syria, Jordan, Saudi Arabia, Turkey and Cyprus.

### New Warner factory in Dublin

A new Warner-International Group factory was officially opened in Dublin on June 29 by the Irish Minister for Industry and Commerce, Mr. John Lynch. It is the latest step in the growth of this American company which already has a £2 million plant at Eastleigh, Hants, whence the Irish market has so far been supplied with the Warner Lambert-Hudnut ranges of products.

Mr. L. A. Coombs, managing director of William R. Warner Ltd. of Eastleigh, and now also managing director of the new company—Warner-Lambert (Ireland) Ltd.—referred to the growth-rate of the Irish market, which had made possible " . . . and desirable " the establishment of the new plant on Irish soil.

The full range of the Group's products would be produced at the factory. The small but well equipped laboratory will be concerned not only with quality control but also with research.

" One of the products of this research that is particularly well known to medical men in Ireland," he said, " is *Nardil*, an anti-depressive drug, unknown to the lay public, but evidently very much prescribed in Ireland."

Mr. Coombs said the factory could be enlarged to three times its present size, and that as well as supplying the Irish market it was planned to develop exports from Ireland to overseas countries —particularly those of the Middle East.

The entire staff at the factory, headed by Mr. L. V. Nolan the general manager, is Irish.

### Powders improved with silicones

Work carried out on the treatment of various powdery materials with silicones suggests that powders and granular materials can be made less susceptible to moisture. Properly treated dry powders retain their free-flowing characteristics and do not cake on long-time storage. Dusting tendencies are reduced and the water-repellency imparted by the treatment is an added benefit to powders used in such products as cosmetic or skin medicants—the silicone treatment of baby and face powders appear to give substantial advantages.

Among the materials so far treated by Midland Silicones Ltd. are salt, sugar, chalk, p.v.c. powders, talc, zinc stearate and borax. The method of treatment has been to mix the powder thoroughly with a solution of either MS 200/350cS fluid or MS 1107 in a suitable solvent followed by drying and, in some cases, a short heat cure. The effective concentration needs to be determined experimentally for each powder, but generally 0·5-5% is effective. For example, talc is improved with 1% of MS 200/350cS fluid, while zinc stearate requires approximately 5%. Lower concentrations are often possible with MS 1107.

### Polish instrumentation order

George Kent Ltd., Luton, have received further orders for instrumentation from the Polish importing organisation, Varimex. Special equipment valued at £30,000 for measuring and controlling processes in Polish chemical industries has been ordered, together with equipment by Kent Tieghi S.p.A., of Milan.

George Kent have progressively increased their sales of instruments to Poland over the last 15 years, since the company's mobile exhibition in 1958 visited the country.

### Coalite's profits fall

Following last year's record results Coalite and Chemical Products' profits fell this year. Net profits were £449,083 (£500,997). The total revenue from sales, etc., amounted to £6,414,786 (last year £6,675,081).

The chairman, Comdr. Colin Buist, stated that the reduction was due to the introduction of a 42 hr. standard week and labour disputes.

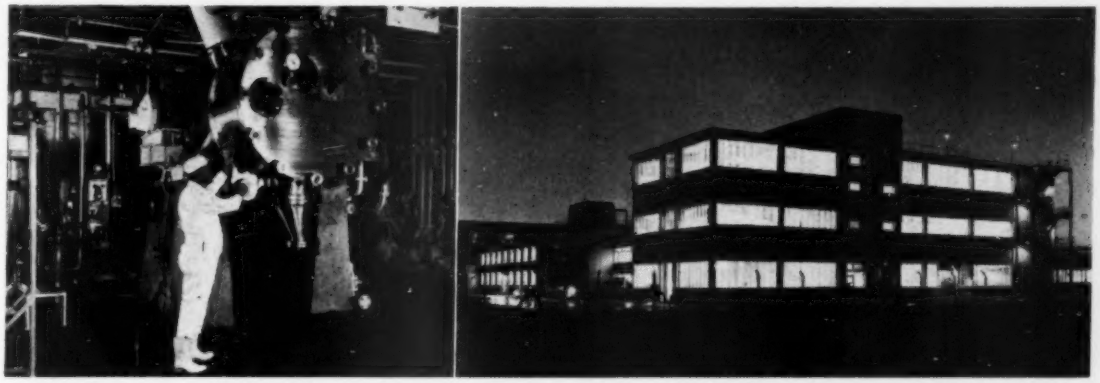
Future expansion includes the building of six new batteries of retorts at Askern and the modernisation of the ancillary sections of the works. This should increase the output by two-thirds. A new large main distillation unit is being installed at the central refinery and it is expected to be commissioned in March next year.

### Sales HQ

G. A. Harvey and Co. (London) Ltd. have opened a new head sales office and showroom in Villiers House, Strand, London, W.C.2. They are on the first floor of a modern office building and cover 6,500 sq. ft. In the showroom are exhibited many items from the Harvey and Harvey-Milner ranges of steel office furniture and partitioning, while in the reception area are coloured transparencies showing examples of production from Harveys' other departments.

### Aromatics refinery

British Celanese Ltd. have appointed L. A. Sim and Co. Ltd. as the sales agents for nitration grade toluene. The new aromatic solvents plant at Spondon will be on stream by mid-September and substantial quantities of toluene will be available for delivery against contract from October 1.



**Left: Plant where antibiotics are extracted. They are then processed to sterile, pure antibiotics in the crystallisation building (right), where new automatic equipment for processing antibiotics has been installed; the extraction building and pharmacological research laboratory are on the left.**

# Automation in Antibiotics Production: Distillers' £500,000 Project

A £500,000 extension of plant and research facilities has just been completed by the Distillers Co. (Biochemicals) Ltd. at Liverpool. It has taken about two years to complete and consists of:

A crystallisation plant which introduces a number of new automatic techniques for processing antibiotics.
An extraction plant and
A new pharmacological research laboratory.

These new installations will increase research facilities and provide unique handling procedures which can be developed specifically for antibiotic processes.

The extraction plant is designed for the production of intermediate antibiotic solutions which are then passed to the crystallisation building for automatic processing. The project was designed jointly by DC(B)L technical staff and D.C.L. engineers with the objective of crystallising the antibiotics and processing them by automatic equipment to produce sterile, pure antibiotics ready for filling into small vials. At no stage are the antibiotics exposed to contamination. Indeed, the building has been constructed to seal off the processing and sterile areas. The few operators required to control the automatic equipment observe precautions for scrupulous cleanliness similar to those taken in the sterile filling areas.

The units of equipment have been installed in such a way that all the motors, the drive gear, and most of the complicated control mechanisms are sited outside the sterile area of the building. In this way they can be maintained easily without endangering the aseptic precautions taken in the processing area. Large volumes of inflammable solvents are used in the crystallisation operations, therefore special safety precautions have to be taken. Most of the solvents used are manufactured by other D.C.L. plants. Over 10,000 gal. of apyrogenic distilled water will be used each week; this will be mainly for the purpose of washing down equipment prior to sterilisation and to ensure complete cleanliness and freedom from pyrogenic material.

Most of the equipment was specially designed and made in Britain; it is the very latest of its kind and the crystallisation building has been planned to permit major extensions or modifications to plant or processes without altering the basic construction of the plant itself. This unusual flexibility will enable the plant to be realigned quickly should the occasion arise.

**Pharmacology laboratory.** Last year the British pharmaceutical industry spent about £6,250,000 on research and employed about 1,400 graduates and 2,600 others on this work alone.

The DC(B)L pharmacological research laboratory will play an important part in the search for new drugs and better remedies. It has increased the company's facilities for screening new substances, including synthetic drugs, and testing existing products. The chemotherapy unit will test drugs for their effectiveness against bacteria and parasitic infections; the pharmacodynamics unit will determine the action of drugs on physiological processes; the biochemical unit determines the absorption and fate of the drugs, while the pathological unit is equipped for testing drugs for pathological properties before they can be released for clinical trials. The pharmacological laboratory has a special section dealing with radioactive tracer techniques.

This latest investment by DC(B)L, allied to the considerable sums of money which are already being spent by the company on research and development, will help it to maintain its position as one of the leading British pharmaceutical companies.

### Fire prevention week

Action committees, comprising council members, business men and other leading citizens, are being set up under the guidance of fire authorities in local areas to organise National Fire Prevention Week from October 30 to November 4 this year.

Sponsors are the Fire Protection Association and The Royal Society for the Prevention of Accidents (RoSPA).

### Expanding storage facilities

A new stores building for Stafford Allen and Sons Ltd. is being erected at Long Melford, Suffolk. The storage facilities will cover 23,000 sq. ft. floor area and the new building has been designed to allow for extensions. It has a steel frame and a double-span roof, each span of which is 60 ft. with wall and central supports only, allowing for maximum cubic use and manœuvring space for fork-lift trucks, loading and storage. The new building will house spices, crude drugs and other raw materials required by Stafford Allen.

### New glass factory

Q.V.F. Glastechnik GmbH., German subsidiary of Q.V.F. Ltd., industrial engineers in glass, are building a new 41,000 sq. ft. factory at Wiesbaden-Schierstein.

# News from Abroad

## WEST GERMANY

### New aromatics plant

Plans for construction of an aromatic chemicals plant at Dinslaken have been confirmed in an announcement by Standard Oil Co. of California and B.P.

It will be operated by a new partnership, BP Benzin und Petroleum A.G. und California Chemical G.m.b.H., to be known as Deutsche BP und California.

The contract for the construction of the plant has been awarded to Lurgi. Completion is scheduled for mid-1962.

Feedstock will be supplied from the adjoining BP Ruhr refinery. The plant will have a designed capacity of 14,000 metric tons of high purity paraxylene employed in a wide field of manufacture, including synthetic fibres, fabrics, films and plastics.

It will use a manufacturing process developed by the California Research Corp., research subsidiary of Standard Oil.

The Dinslaken project parallels a similar venture in the U.K. which involves construction of a large aromatics plant in Kent. The two ventures involve £7,000,000.

## AUSTRALIA

### British 'flu drug on market

*Virugon*, made in the U.K. by Winthrop Laboratories, is shortly to be made in Australia under the name *Vironil*. It will be manufactured by Winthrop Laboratories, a division of Sterling Pharmaceuticals Pty. Ltd.

The drug, which is an oral anti-viral agent, is the result of ten years' research, much of which was undertaken in Sweden.

## SOUTH AFRICA

### First citric acid plant

A £500,000 factory for the production of citric acid will be erected in Natal near Durban, within the next 12-15 months. The project has been announced by D. Martin, a Johannesburg industrialist and managing director of the company which is backing the project.

The plant will be built by a German firm. A team of engineers from its factory is expected to arrive soon for preliminary work on the project.

When in full production, the new plant is expected to save South Africa about £400,000 a year in foreign exchange. At present citric acid is being imported. The plan is to manufacture the chemical by a new patented process from sugar-cane molasses.

The competitive manufacturing cost will enable the company to seek export outlets for a surplus of about 650 ton/yr. There is a potential export market for about 900 ton/yr., and the yield in foreign earnings would be £200,000. The maximum output of the plant would be 2,400 ton/yr. but the plan is to produce 2,000 tons for the first few years. The estimated annual consumption in South Africa at present is about 1,350 tons.

## NIGERIA

### I.C.I. factories

I.C.I. is to build two plants with a capital investment of approximately £½m. in Western Nigeria to manufacture paints and plant protection products. If negotiations are successful the plants will be built at the Ikeja Industrial Estate outside Lagos. This will be I.C.I.'s first manufacturing venture in Nigeria, where I.C.I. (Export) Ltd. was recently established.

## FRANCE

### Dijon plant for I.F.F.

Insufficient space for expansion in their French plants at Bois Colombes (management, administration and flavour manufacture) and Courbevoie (perfumery manufacture) has necessitated I.F.F.'s acquisition of a 10-acre site in Dijon for building a flavour plant. Dijon is a fruit growing centre, important to I.F.F. for the manufacture of their concentrated fruit juices and flavours.

The vacated premises at Bois Colombes will be converted and equipped for the perfumery department. The main centre of the French I.F.F. company, administration, development laboratories and sales offices, both for flavours and perfumery, will remain at Bois Colombes.

## HOLLAND

### Tall oil plant

N.V. Chemische Fabriek Naarden of Holland and Kemi Oy of Finland have signed a preliminary agreement with Union Bag-Camp Paper Corporation, U.S.A. A jointly owned company will be set up to build a fractional distillation plant in Holland, the first such plant within the European Common Market.

The proposed company will be established under the name Naarden-Kemi. The plant will be at Wormerveer, Holland, on a site owned by a Naarden subsidiary. About $1·7 million is involved in this new project. The installation, which will be built along the lines of the tall oil distillation operation at Union-Camp's Savannah, Georgia, plant, is expected to come on stream in two years' time.

The products derived from the fractional distillation of tall oil, such as fatty acids and resins, are base materials. They are used in making artificial resins, paints, enamels, rubber, asphalt, linoleum, soap and industrial greases and are essential raw materials for the paper, metal and mining industries.

## AUSTRALIA

### Industrial chemicals merger

Dewey and Almy Pty. Ltd. has formed a new company with W.J. Manufacturing Co. Ltd. to manufacture industrial chemicals at Brookvale near Sydney. Authorised capital is $1,400,000.

Dewey and Almy Pty. Ltd. is a subsidiary of W. R. Grace and Co. Inc.

## ITALY

### Marchon's factory opened

Marchon Products' new plant in Northern Italy, to be operated by their totally owned subsidiary Marchon Italiana S.p.A., is now in production in Castiglione delle Stiviere (Mantova). The plant produces surface active agents for industrial and cosmetic uses. Almost the whole Marchon range of products will be manufactured in Italy, with the exception of household detergent powders, sodium tripolyphosphate and fatty alcohols.

The new factory is on a 20-acre site bordering the Brescia-Mantova highway and is well served by motorway and railway connections.

## HOLLAND

### I.C.I.'s first plants at Rotterdam

The first manufacturing project in the Common Market to be undertaken by I.C.I., since the announcement in February of their intention to expand in Europe, is to be in plastics.

They intend to erect plants for the manufacture of *Perspex* acrylic sheet and *Diakon* acrylic moulding powder, and for methyl methacrylate, from which they are made. £7 million will be spent on the 300-acre site, to be known as the Rozenburg Works, which I.C.I. is leasing at Rotterdam.

## BRAZIL

### Dehydrogenation unit

Petroleo Brasileiro S.A. (Petrobras) has been licensed by Houdry-Brazilian Co. to construct a 29,000 metric ton/yr. dehydrogenation unit near Rio de Janeiro.

The Houdry unit will be situated at Petrobras' synthetic rubber complex now under construction at Duque de Caxias. The plant will produce butadiene, the principal ingredient in synthetic rubber, from normal butane or mixtures of butane and butenes. Feedstocks for the Houdry dehydrogenation plant will be furnished by Petrobras' new refinery at Duque de Caxias.

In addition to the dehydrogenation unit, Petrobras has licensed two large Houdriforming units which are now under construction near Rio de Janeiro and Sao Paulo.

. . . in the Organic and Fine Chemicals Laboratory. There are lots of other girls in all sorts of jobs and I must say they all seem very happy at Berk. But I'm told it's always been the same here, ever since we started ninety years ago. I'm a control lab. analyst, testing chemicals used in anything from cosmetics to cleaning agents and in industries as different as agriculture and road building. Part of my own duties is to determine the purity of potassium bromate used in such contrasting end-products as a neutraliser for "cold perms" and an anti-shrink agent for the woollen trade. And I know our chemicals are used in lots of other things—food and rubber and plastics and soaps and textiles and leather and greases and fuel oils and goodness knows what else. There must be scores of applications of which I've never even heard. As one of our chemists says—"When it comes to serving industry, Berk serves nearly everyone."

*If you need information or advice on any chemical problem, ask Berk about it. Somewhere in the wide range of Berk literature, the answer may already exist; and if it does not, Berk experts will gladly set to work to find it. Write or telephone:*

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MANCHESTER · GLASGOW · BELFAST · SWANSEA

### Aerosol hair spray with refillable container

The novel feature of a new aerosol hair spray, *Go Gay*, is a refillable purse dispenser that can be replenished from the standard pack. The purse dispenser is a glass bottle which fits into a metal outer container. This itself is an innovation in this country, where plain glass aerosol containers have not hitherto been used. The makers of *Go Gay*, Misgo Products Ltd., say the glass containers are imported and are specially tested to withstand extra pressure. The purse container is fitted with a special valve (also imported) which is inserted into the valve of the "mother" container and fills in a few seconds.

The hair spray is based on polyvinyl pyrrolidone and has a high content of lanolin. Because of this it is claimed to disappear from the hair in a few hours, leaving the hair free of accumulated resin, which is a bad feature of poorly formulated sprays. The product is being promoted as "the world's first vanishing hair spray."

Misgo Products is a new company jointly owned by Helene Curtis Inc., the third largest toiletries house in America, and J. L. Morison Son and Jones Holdings Ltd., who market pharmaceutical products in Britain and abroad. Managing director of Misgo Products is Michael Ogle, who has been associated with J. L. Morison Son and Jones for ten years. It is planned to launch other Helene Curtis products in this country in due course. Misgo have a factory at Hemel Hempstead, Herts.

*Go Gay* retails at 12s. 6d., giving the retailer a profit of 3s. 1½d. As an introductory offer the purse dispenser is being given free with the large container. Three grades—for normal, dry and oily hair—are available.

### Two in one antibiotic injection

The Distillers Co. (Biochemicals) Ltd. have introduced *Soluwone*, an antibiotic injection which combines the antibacterial actions of crystalline penicillin and streptomycin. Each single-dose vial contains 500,000 units penicillin (sodium salt) B.P. and streptomycin sulphate B.P., equivalent to 0·5 gm. base. Multi-dose vials containing five doses are also available.

With *Soluwone* two new vials of improved design have been introduced: a general purpose injection container for the lower strength and a new type of multi-dose container.

Among other applications *Soluwone* is indicated in mixed infections due to Gram-positive and Gram-negative pathogens against which it presents a bactericidal attack. Rapid peak levels are provided by the combination, ensuring an immediate therapeutic concentration

**New PVP hair spray in aerosol pack with refillable purse dispenser.**

to control the invading pathogens. Owing to the dual action development of resistant strains may be delayed.

Packs and prices are as follows:

Single-dose vials, pack of 5 8s. 9d. (Trade);
Five-dose vials, pack of 10 66s. 8d. ex. P.T.

*Soluwone* is subject to Part II of the Therapeutic Substances Act and may be supplied upon prescription only.

### Aerosol dry cleaner

Goddards of Leicester have marketed *Aero Dry Clean*, an "instant" stain remover. Aerosol-packaged, it is claimed to remove oil, grease, and most beverage and food stains from natural fibres as well as from such materials as rayon, artificial silk and the acetates. The product is a new compound of solvents mixed with a fine powder which quickly soaks up the stain and is then simply brushed off. It does not contain acetone, which would damage artificial fibres.

*Aero Dry Clean* will retail at 5s. 6d. (wholesale—45s. per dozen). It is packed in one-dozen corrugated outers.

### Potato blight control

A new chemical control for potato blight is announced by Boots. Based on *Polyram* Combi*, it is Boots Potato Blight Spray, which underwent extensive field trials in many parts of Britain last year. It is claimed that these trials showed that the new product is equal to or more effective than all the recently introduced blight controls and costs considerably less.

For application the powder base for the spray should be creamed before being added to the water in the spray tank. The spray should be applied a day or two before blight normally occurs. The second spray should be applied 14-21 days later according to the growth of the crop and the weather. If the weather remains warm and humid the new product should be sprayed at fortnightly intervals until the crop is "down," but if it is dry and cold the spray is applied at intervals of three weeks. Trials revealed that for optimum control a minimum of three sprays is required. Finally, the tops are burnt off either with sodium chlorate or a proprietary potato haulm destroyer.

The active ingredient of Boots Potato Blight Spray is recognised by the Ministry of Agriculture as a non-toxic chemical, but the usual precautions should be taken when handling.

Supplied in a pack of ten 2 lb. packs, which is sufficient to treat 10 acres once, Boots Potato Blight Spray costs 170s., that is 17s. per acre with proportionate price reductions for bulk orders.

* Registered trade mark of BASF Ludwigshaven.

### Inhalation therapy

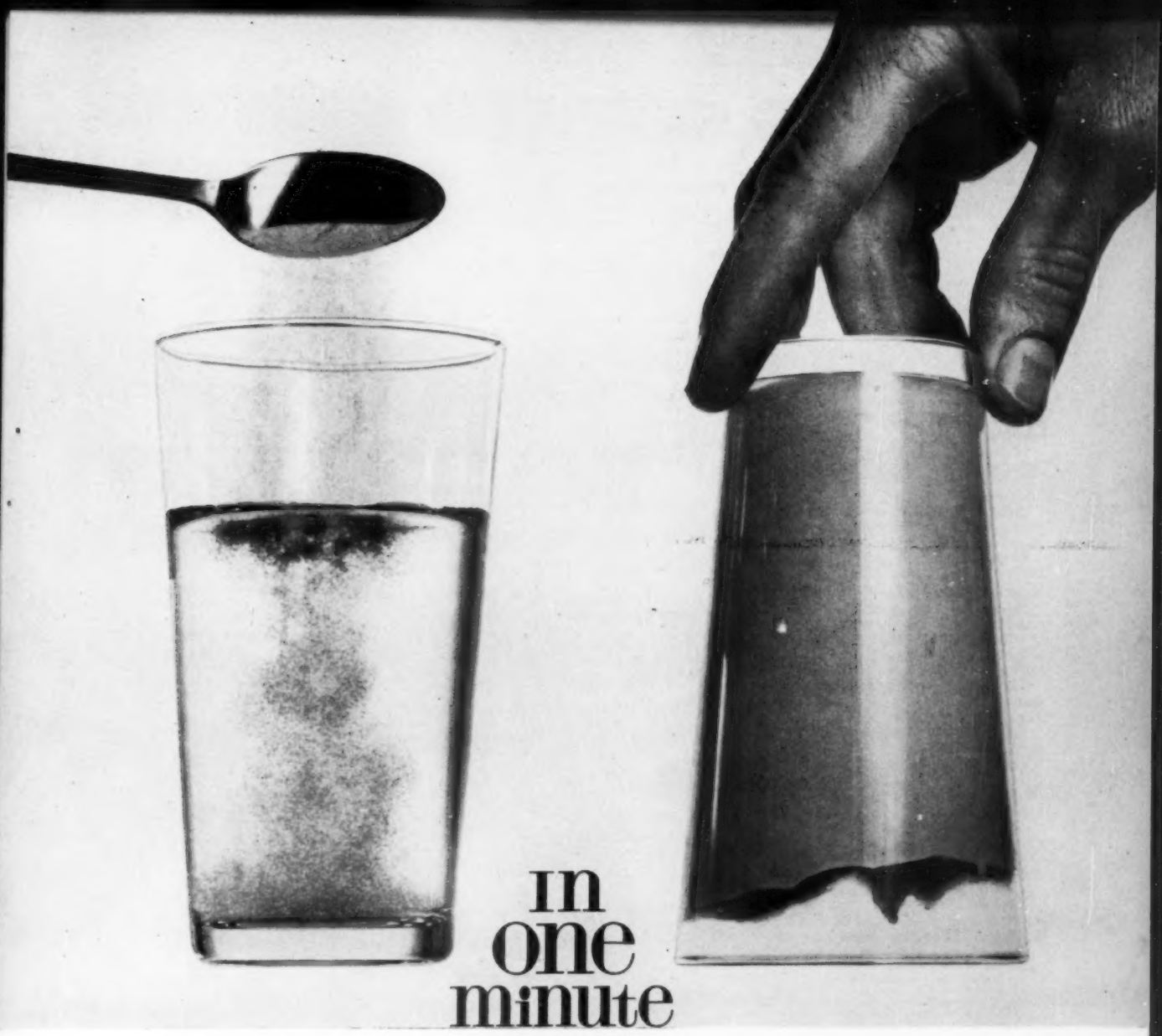
The *Climamask* is a new device for inhalation therapy introduced in the U.K. from Germany by W.E.D. Distributors. It has a plastic face-piece attached to an electrical heating chamber. Air drawn through the container is heated to 100°-126°F. A wick impregnated with pine oil fits into the apparatus and gives the inhaled air a pleasant, invigorating aroma. A doctor writing in the *Nursing Mirror* states that there are good reports on the effectiveness of the apparatus for relieving respiratory ailments such as asthma, bronchitis and colds. He suggests that other therapeutic agents might be tried instead of the pine oil. The facepiece can be removed and sterilised. Including a bottle of pine oil and a headband, the mask retails at £4 15s.

### Vaseline cream shampoo

Chesebrough-Pond's have launched a new Vaseline shampoo, packaged in lilac-coloured foil sachets and polythene tubes. The shampoo itself is lilac-coloured and delicately perfumed. It contains sweet almond oil and is said to be specially suitable for dry hair. Prices are 9d. per single-shampoo sachet and 2s. 11d. for a 5-6 shampoo tube.

### Eye treatment

Ward, Blenkinsop and Co. Ltd. have announced *Mydrilate* (cyclopentolate), which produces cycloplegia and mydriasis of rapid onset and comparatively short duration. It is claimed to be non-irritant, sensitisation is rare, and its effects can be readily reversed by miotics. *Mydrilate* is supplied in two strengths: 0·5% solution in 15 ml. dropper bottles at 9s. (retail) plus 1s. 6d. P.T., and 1% solution in 15 ml. dropper bottles at 10s. (retail) plus 1s. 8d. P.T.



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## NEW PATENTS

COMPLETE SPECIFICATIONS ACCEPTED

**Miscellaneous**

Method of manufacturing boron nitride. *United States Borax and Chemical Corporation.* 870,084.

Manufacture of organic peroxides. *Farbwerke Hoechst A.G.* 870,118.

Diethinylquinols and a process for their manufacture. *Farbwerke Hoechst A.G.* 870,097.

Preparation of active oxide. *Kali-Chemie A.G.* 870,172.

3-carboxy-4-methyl-naphthalene derivatives and a process for preparing them. *Farbwerke Hoechst A.G.* 870,384.

Production of cumene hydroperoxide. *Soc. des Usines Chimiques Rhône-Poulenc.* 868,907.

Amino-naphthol derivatives. *Farbenfabriken Bayer A.G.* 868,884

Preparation of monomethylamine nitrate. *Commercial Solvents Corporation.* 870,435.

Amino-trifluoro-toluene-disulphonyl compound and the production thereof. *Olin Mathieson Chemical Corporation.* 870,576.

Iodine-containing aminobenzoic acid amides and a method of producing same. *Österreichische Stickstoffwerke A.G.* 870,321.

Process for producing sodium zeolite A. *Union Carbide Corporation.* 870,440.

Aliphatic glycidyl ethers and the preparation of sulphonates therefrom. *Thomas Hedley and Co. Ltd.* 870,456.

Process for preparing acid esters of polyphosphoric acids and their salts. *Farbwerke Hoechst A.G.* 870,098.

Preparation of halogenated phenoxyalkyl substituted amines. *Rohm and Haas Co.* 870,399.

Method for the purification and concentration of carboxylic acids. *Joh. A. Benckiser G.m.b.H.* 868,926.

Manufacture of nitric acid. *M. E. J. Cathala.* 869,062.

Cyclohexene compounds and process for making same. *International Flavors and Fragrances Inc.* 868,850.

Glycolic acid compounds and production thereof. *Recherches et Techniques Appliquées.* 870,441.

New patents are from the *Journal of Patents*, and new trade marks are from the *Trade Marks Journal*. In each case permission to publish has been given by the controller of Her Majesty's Stationery Office. Each of the publications mentioned is obtainable from the Patent Office, 26 Southampton Buildings, London, W.C.2.

## NEW TRADE MARKS

APPLICATIONS

**Pharmaceuticals**

METORALANE.—810,067. *Société Commerciale d'Applications Industrielles.*

VIPROMAL.—810,269. *Winthrop Group Ltd.*

EYEDREXIN.—810,695. *Phillips, Scott and Turner Ltd.*

NEOPULMO - BAILLY. — 810,885. *Bailly Ltd.*

KEFALOS.—B812,140. *The Distillers Co. (Biochemicals) Ltd.*

DIVACNE.—812,210; SELZAVIT.—812,212. *Diva Laboratorium A.G.*

LUCOFEN.—813,155. *H. Lundbeck and Co. A/S.*

LONZA.—813,595. *Lonza Electric and Chemical Works Ltd.*

SOLCOHEPSYL.—813,683. *Solco Basel A.G.*

NONOCAL 900.—815,632. *Horlicks Ltd.*

CORTEPYROL.—816,361. *Aktiebolaget Bofors.*

NUMORIL.—816,520. *The British Drug Houses Ltd.*

POLIFORT.—816,903. *Merck and Co. Inc.*

KANNAPEN.—816,904; BOVOLON.—817,846; GINA.—818,071. *Winthrop Group Ltd.*

NORCOF.—817,474. *Norchem Ltd.*

SCLERAX.—798,114. *Roche Products Ltd.*

BENCLEX.—802,776. *Glaxo Laboratories Ltd.*

GERMOTOL.—803,810. *Bushman and Kaydot Ltd.*

RADANIL.—807,209. *Roche Products Ltd.*

GLUCOTROL.—808,812. *The Wellcome Foundation Ltd.*

THERAFLU.—809,011. *Sandoz Products Ltd.*

CALMEDINE.—810,613. *Société Commerciale d'Applications Industrielles.*

HEPATOKINEX.—810,652. *Laboratoires Badrial S.A.*

DYSMENS.—810,690. *Winthrop Group Ltd.*

LITHRADERM.—810,970; VILIQUID.—810,972. *Desitin-Werk Carl Klinke G.m.b.H.*

DRAZINE.—811,965. *T. J. Smith and Nephew Ltd.*

KEFALIN.—812,139. *The Distillers Co. (Biochemicals) Ltd.*

CARDIORYTHMINE.—813,890. *Biofarma S.A.*

## NEW COMPANIES

These particulars of new companies have been extracted from the daily register of Jordan and Sons Ltd., company registration agents, Chancery Lane, London, W.C.2.

**Liberty Pharmacies Ltd.** 23.6.61. Macrom House, Seymer Road, Romford. To take over the bus. of retail chemists and druggists etc. cd. on at Romford and Chelmsford by Macarthy's Ltd. £100. Dirs.: Alan R. Ritchie and Albert L. Slow.

**Marylebone Pharmacal Co. Ltd.** 20.6.61. Mnfrs. and dlrs. in drugs, etc. £100. Dirs. not named. Subs.: Robert Banks and F. J. S. Waller, Essex House, Essex Street, London, E.C.2.

**Newhaven Pharmacies Ltd.** 23.6.61. 133 Windsor Lane, Slough. £100. Dirs.: Fred Brown and L. J. F. Preddy.

**E. Stewart Brown Ltd.** 12.5.61. 70 The Highway, New Inn, Pontypool, Mon. Chemists. £1,000. Dirs.: Edward S. and Joan M. Brown.

**Parnosa of London Ltd.** 15.5.61. Harland Trading Estate, Honeypot Lane, Stanmore. Chemists. £100. Dirs.: Sydney, Anthony C. and Rachel Levy and L. W. Cash.

**R. H. Mascall Ltd.** 15.5.61. Atlas Chambers, King Street, Leeds 1. To take over bus. of a pharmaceutical chemist cd. on at 82 Otley Road, Leeds, by R. H. Mascall. £15,000. Dirs.: Ronald H. and Edith M. Mascall.

**Woodberry Chemists Ltd.** 15.5.61. £100. Dirs.: Mrs. Ann Westwood, 15 Worcester House, Bishop Bridge Rd., London, W.2., and Lucjan Dziarski.

**Pharmacy Products (U.K.) Ltd.** 16.5.61. 79 New Bond Street, London, W.1. £100. Dirs.: H. E. J. M. and Madeleine A. M. Meunier.

**J. Spensley Ltd.** 16.5.61. 1 Twydall Green, Gillingham, Kent. Chemists. £100. Dirs.: John C. and Winifred Spensley.

**Ryehill Chemists Ltd.** 17.6.61. 25 Market Place, Huddersfield. £3,000. Dirs.: Malcolm R. Thirkill and Miss Rita Newstead.

**Hamlets (Chemists) Ltd.** 18.5.61. 13B Brookmead, Hildenborough, Kent. To take over the bus. of retail dispensing chemists cd. on at 72/4 High Road, Woodford Bridge, Essex, by N. E. and Mrs. P. M. Hamlet. £10,000. Dirs.: N. E. and Mrs. P. M. Hamlet.

**Walkden Pharmacy Ltd.** 18.5.61. 4 Hodge Road, Walkden, Lancs. £1,000. Dirs.: David Swerling and Gerald M. Morris.

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**From MANUFACTURING CHEMIST**
**August 1896**

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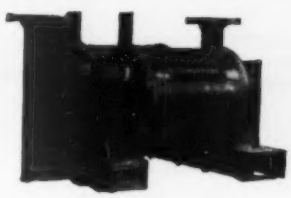
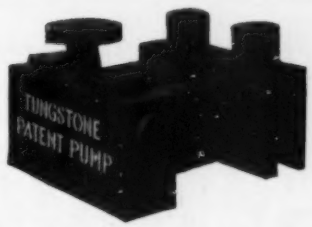


non-immersion **LEAD PUMP.** Made in 8 capacities: 375, 600, 800, 1,200, 1,500, 2,000, 3,000, 3,600 gallons/hour.

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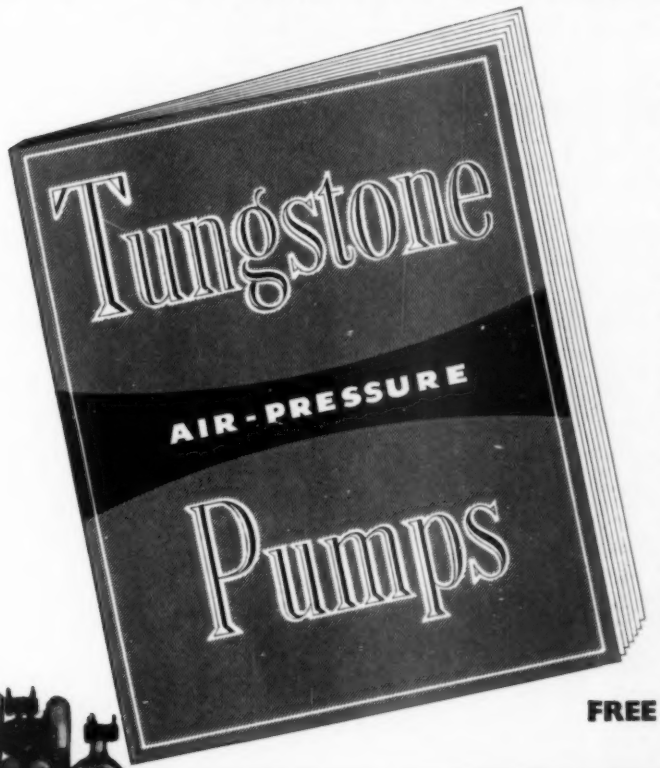
# TUNGSTONE PUMPS

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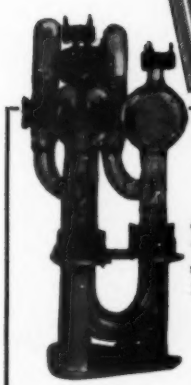

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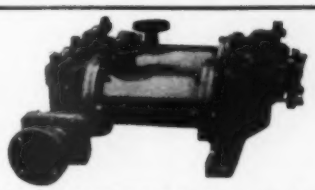

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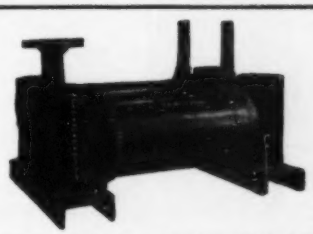

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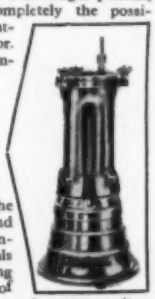

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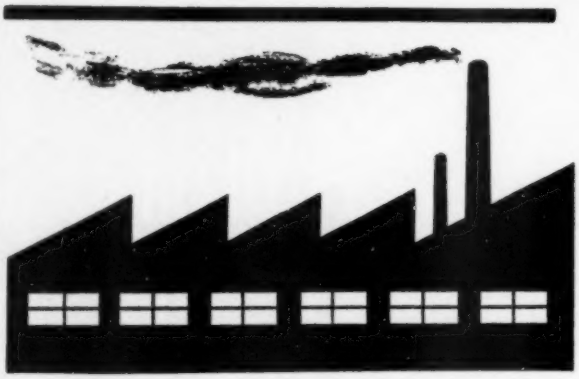

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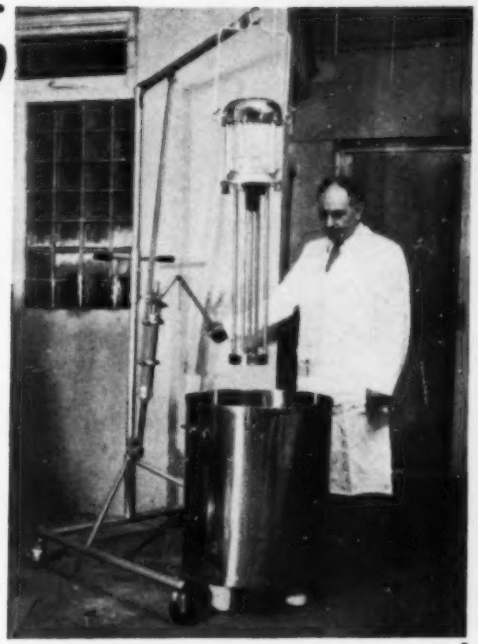

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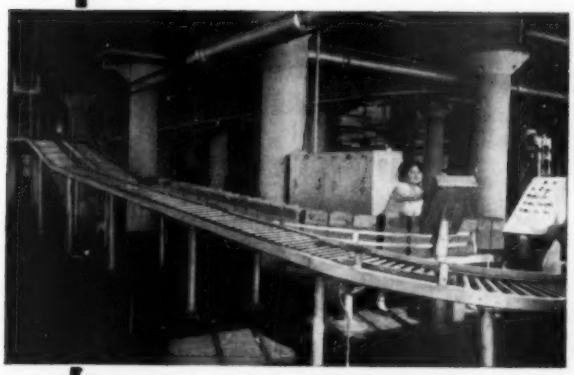

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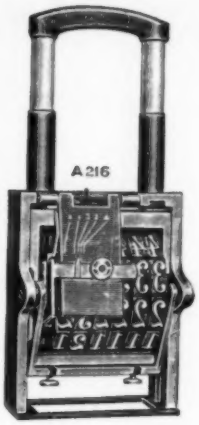


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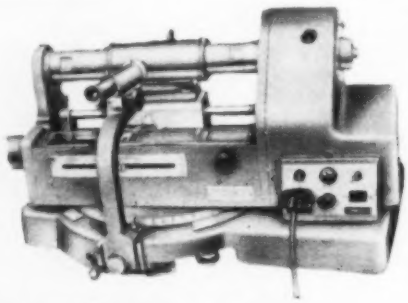

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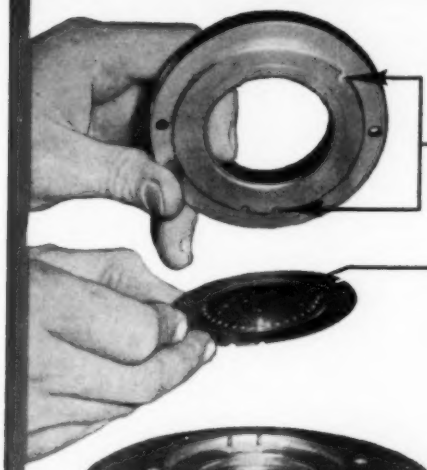

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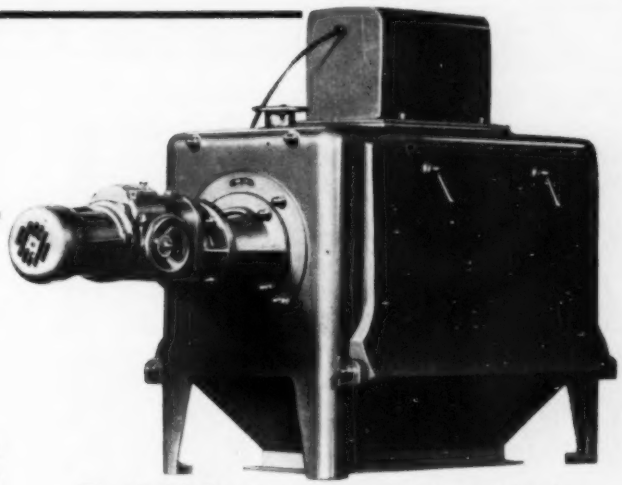

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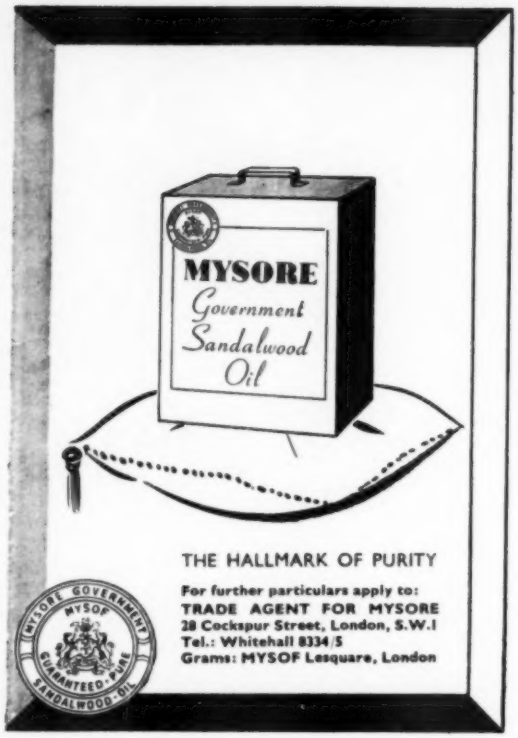


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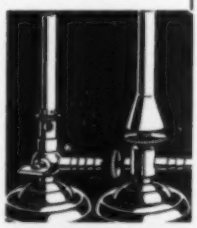

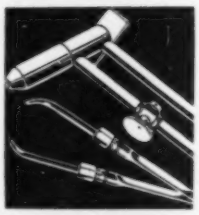

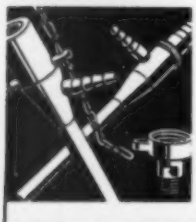

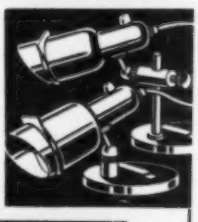

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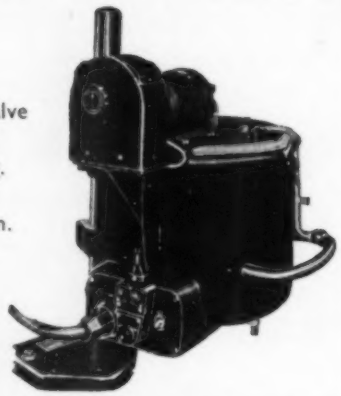

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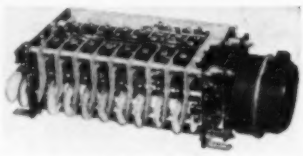

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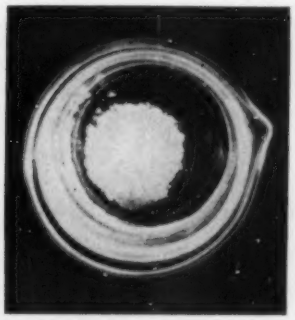

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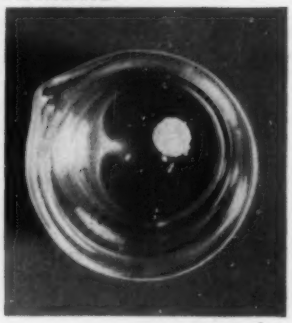

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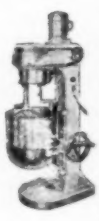

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*(Continued on page A70.)*

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**Ref. B.445.** British. Male. Married. Age 42. Indentured apprentice. 2 yrs. Senr. Jig & Tool D/man, mnfrs. domestic & industl. ventilating equipt. 4 yrs. Senr. Jig & Tool Designer, mnfrs. marine diesel engines, rotary filters, industl. boilers & genl. engrs. 1½ yrs. Chief Jig & Tool Designer, consultant engrs. & contract designers. At present Chief Jig & Tool Designer, light engrs. Seeks post as **CHIEF JIG / TOOL DESIGNER.** London/Middx. £1,300 p.a. min.

**Ref. B.446.** British. Male. Married. Age 36. Inter. B.Sc. Chem., Applied Maths., C. & G. Leather mnfr. & dyeing certs. At present Experimental Officer/Dyestuffs Technologist in Tech. Service Dept. of dyestuffs concern. Consid. exper. leather & fur dyes, use of pigments in paints & printing inks, evaluation of new products & competitive materials, technical liaison. Good knowledge electronics. Seeks **SUITABLE APPOINTMENT (NOT LEATHER TRADE)** in non-city area of N. England, Scotland or N. Ireland. £970 p.a., but pleasant surroundings more important than salary.

**Ref. B.447.** British. Male. Married. Age 32. H.N.C. Bldg. & Civil Engg., Grad. Inst.Struct.E. 3 yrs. Foreman Joiner, bldrs. 7 yrs. Foreman & Clerk of Works, govt. dept. At present Structural Designer, structural steel mnfr. Consid. exper. site supervision, estimating, work measurement, genl. bldg. design. Seeks post as **STRUCTURAL DESIGNER OR CIVIL ENGINEER.** London or Watford. £1,200 p.a.

**Ref. B.448.** British. Male. Married. Age 29. H.N.C. Mech. Dip. in Refrigeration, C. & G. Full Tech. Cert. in Refrigeration, A.M.Inst.R. 5 yrs. Technical Trainee, refrigerator mnfr. 5 yrs. Refrig. Mechanic, army. At present Experimental Engr., mnfr. refrigerating equipt. Consid. exper. supervision of instlln., maintenance & repair refrig. equipt., & of large cold store & ice-making plant. Seeks post as **REFRIGERATION ENGR.—TECHNICAL OR ADVISORY.** Central or N.W. London. £1,250/£1,400 p.a.

**Ref. B.449.** British. Male. Married. Age 30. 2 yrs. Sales Correspondent/Asst. Buyer, battery mnfrs. 5 yrs. Buyer, furnace mnfrs. & genl. sheet metal & machining. Seeks post as **BUYER (ENGG.) OR SALES REPRESENTATIVE.** Hampshire/Surrey/Sussex. £850/£1,000 p.a.

**Ref. B.450.** British. Male. Married. Age 32. H.N.C. Prod.E. 1 yr. Detail D/man, civil engg. 3½ yrs. Devpt. D/man, telecomm. & electronic engg. 2 yrs. Designer & 3 yrs. Section Leader, mech. design section, electronic & microwave engrs. At present Section Leader, electronic, microwave & light precision engg. Seeks post as **DESIGN ENGR./LIAISON** between elec. & electronic design & D/O. for Mech. Design. U.K. £1,400 p.a.

**Ref. B.451.** British. Male. Married. Age 32. B.Sc. (Applied Chem.), Ph.D. (Organic Chem.). 2½ yrs. Devpt. Chemist, medicinals mnfr. At present Prod. Chemist, fine chemicals mnfr. Seeks **CHEMICAL PROD./PLANT OR PROD. MANAGEMENT POST.** £1,600 p.a.

**Ref. B.453.** British. Male. Married. Age 48. Nat. Inst. Engg. Dip. Planning, Estimating & Ratefixing. 4 yrs. Maintenance Handyman, wine & spirit merchant. 5 yrs. Fitter & Elec. Welder, elec. engrs. 12 yrs. Brass Finisher & 6 yrs. Charge Hand, light engg. At present Foreman of Spraying, Assembly & Test with light engg. concern. Seeks post as **FOREMAN OR RATE FIXER.** London. £16 per week.

**Ref. B.454.** British. Male. Married. Age 33. H.N.C., A.M.I.Prod.E. 11½ yrs. Apprentice/D/man/Planner/Estimator, aircraft mnfr. At present Chief Prod. Engr., ceramic resistor mnfrs. Seeks post as **ASST. WORKS MANAGER/PROD. MANAGER/PROD. ENGR.**—not aircraft industry. Kent, Surrey, Sussex, Berks, Bucks or Hampshire. £1,500 p.a.

**Ref. B.456.** British. Male. Married. Age 33. H.N.C. (Mech. Eng.), A.M.I.Mech.E. 2 yrs. Workshops Trainee, precision engrs. 3 yrs. D.O. Training, genl. mech. engrs. 5 yrs. Design Officer, paint mnfrs. 5 yrs. Project Engr., nuclear engg. At present Project Engr., nuclear engg. Good knowledge chem. plant & pressure vessel design. Seeks post as **PROJECT OR DESIGN ENGR.** London or within 30 miles radius W. of London. £1,600 p.a.

**Ref. B.457.** British. Male. Married. Age 31. Hons. Dip. Agric. Eng., 1st Class Dip. Automobile Eng. with hons. for practical work, C. & G. Motor Vehicle Technicians Work (Advanced) Cert. 1 yr. Pupil Farmer. 1½ yrs. Tractor Driver/Mechanic, agric. committee & agric. contractor. 10 mnths. Tractor Driver/Mech., inst. of agric. botany. 6 mnths. Mechanic/Welder, motor engr. 2 yrs. Manager's Asst., motor garage. At present Field Officer (Agric.), Officer i/c Workshops of special devpt. section of govt. agric. dept., Africa, concerned with devpt. of new forms of agric. m/cy. Seeks **AGRIC. OR AUTOMOBILE ENGG. POST**—Devpt. and Modification of existing designs/Workshop Manager/Maintenance Engr. Australia—pref. Queensland. £2,000 p.a.

**Ref. B.458.** British. Male. Married. Age 38. O.N.C. Elec., H.N.C. Prod. Engg., A.M. Oil and Colour Chemists. 6 yrs. Engg. Trainee, 6 mnths. Tech. Engr., 1 yr. Prod. Engr., 8 yrs. Devpt. Engr. & 4 mnths. Senr. Project Engr., & consultant, electro/mech. engrs. At present self-employed Consultant Engr. Holds several patents mostly applications of plastic materials, electro/mech. component construction. Seeks **PRODUCTION DEVPT. OR MANAGEMENT POST.** London or Home Counties—pref. Herts or Surrey. £1,500 p.a. min.

**Ref. B.459.** British. Male. Married. Age 45. Matriculation dinstinctions, maths., physics, chem. 3 yrs. Junr. Clerk, 2 yrs. Claims Settlement Broker, insurance brokers. 1 yr. Correspondence/Actuarial, insurance brokers. At present Company Director—buying, management, costing, cash control—scrap metal processors & merchants. Consid. exper. Estimating & Negotiation of contracts, costing, instlln. of new processes, yard & personnel management, plant maintenance & renewals, cash control & private ledger. Seeks **EXECUTIVE/MANAGERIAL POST.** U.K. £1,200 p.a.

**Ref. B.460.** British. Male. Married. Age 36. O.N.C., H.N.C. Mech. Eng. with endorsements, Workshop Technology, Principles of Elec., Theory of m/cs. & Industl. Administration. 5 yrs. Apprentice, & 2 yrs. Junr. D/man, aircraft constructors. 4 yrs. Devpt. D/man, motor & aircraft engrs. 2 yrs. Design D/man, bldg. plant mnfrs. 2 yrs. D.O. Checker. At present Senr. Designer, mnfr. electronic & electro-mech. equipt. & instruments. Seeks post as **SENR. MECH. OR ELECTRO-MECH. DESIGNER.** S.W. London or Surrey. £1,100 p.a.

**Ref. B.461.** British. Male. Married. Age 45. Dip. Hort. with distinctions, A.M.I.Biol., A.I.Agr.E. 3 yrs. Manager, market gardening. 1 yr. Horticultural Instructor, agric. instruction. 3 yrs. Horticultural Adviser, land settlement. 3 yrs. Hort. Advisory Officer, agric. instruction. 12 yrs. Vice-Principal, horticultural instruction. At present Senr. Lecturer in Horticultural & Soil Science, agric. & hort-training, & consultant (part-time) in soils & manures & direct trials for agric. consultants. Author of several published books. Seeks post as **CONSULTANT OR INDUSTL. LECTURER.** U.K.—not London. £2,000 p.a.

**Ref. B.462.** British. Male. Married. Age 35. O.N.C., H.N.C., Inter. & Final Dip. in Mang. Studies & endorsements, A.M.I.Mech.E., Grad.I.Prod.E. 4 yrs. Apprentice & 2 yrs. Junr. D/man, mech. engrs. 1 yr. Tech. Asst., pump mnfr. 3 yrs. Planning Engr., chem. plant mnfr. At present Mech. Engg. Design Engr., consultants—mech. & chem. engrs. Seeks post as **PERSONAL ASST.** U.K. £1,300 p.a.

**Ref. B.463.** British. Male. Married. Age 41. H.N.C. Mech. 10 yrs. Senr. D/man, commercial radio & TV. 9 yrs. Designer D/man, radio & radar equipt. 1½ yrs. Section Leader, computors. 2 yrs. Engr. (liaison), guided weapons. At present Section Leader (electro-mech. D.O.), electro-mech. equipt. mnfr. Seeks post as **D.O. MANAGER/CHIEF D/MAN/SECTION LEADER.** London area. £1,300/£1,500 p.a.

**Ref. B.464.** Indian. Male. Single. Age 23. **RESIDENT U.K.** B.E. (Elect.). 6 mnths. Junr. Engr., allocation of H.T. Loads, maintenance of load records, problems of generation & transmission of electricity. 1 yr. Asst. Engr., preparation estimates for cable laying & plant instlln. Just completing post-grad. course & seeks **PROD. POST—PREF. IN CABLE INDUSTRY.** U.K. £750 p.a.

**Ref. B.465.** British. Male. Single. Age 26. H.N.C. Mech. Eng., G.M.I.Mech.E. 6 yrs. Apprentice, maintenance engg. At present Devpt. Engr., control engrs. & instrumentation. Design Office and admin. exper. Seeks post as **PROJECT ENGR.** London. £1,100 p.a.

**Ref. B.466.** British. Male. Married. Age 35. O.N.C. & H.N.C. Mech. & endorsements, Grad.I. Mech.E. 1½ yrs. M/c Setter, munitions. 1 yr. Fitter, portable electric tool mnfr. 4½ yrs. Aircraft Engr., airline operators. 5 yrs. Research Engr., diesel fuel injection mnfr. 3½ yrs. Research Engr., mining research. At present Research Engr., steam & instrument engrs. Seeks post as **RESEARCH ENGR.** Pref. within 20-mile radius of Chichester. £1,175 p.a. min.

**Ref. B.467.** British. Male. Married. Age 36. O.N.C. Mech. Engg. 17 yrs. from Apprentice to Senr. D/man i/c plotting table, radar ground to air plotting table. 2 yrs. Section Leader of design D/men—with some prod. engg. & liaison duties—instrumentation of rocket site. At present Senr. Design D/man (Mech.) Research, research into medical & pneumatic equipt. Seeks post **"OFF THE BOARD" WITH GOOD ADMINISTRATIVE PROSPECTS.** Within 20-mile radius of Chichester. £1,200 p.a. min.

**Ref. B.468.** British. Male. Married. Age 27. O.N.C. Mech., 1st yr. H.N.C. Mech. 5 yrs. Apprentice, genl. engg. 1 yr. Jig & Tool D/man, & 2 yrs. Tech. Service Engr., air conditioning & refrig. equipt. for aircraft industry. At present Asst. to Sales Manager, equipt. for handling of liquids in bulk. Seeks **TECHNICAL REPRESENTATION/LIAISON POST.** London, Home Counties or S. Coast of England. £900/£950 p.a.

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